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Attorney Docket No. 970113R/HG

**IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE**

Applicant(s): Tomio KIMURA et al

Serial No. : 09/678,218

Filed : September 29, 2000

: 1,2-DIPHENYLPYRROLE
DERIVATIVES, THEIR
PREPARATION AND THEIR
THERAPEUTIC USES

Unit : 1613

Examiner : L. STOCKTON



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**STATEMENT OF ACCURACY OF TRANSLATION
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S I R :

I, the below named translator, state:

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That I am knowledgeable in the English language and in the Japanese language.

Japanese application 8-083562 filed April 5, 1996 is the priority document. A certified copy of said priority document was filed in the PTO on September 12, 1997 in the file of application SN 08/824,775 which issued as USP 5,908,858 (the present application is a reissue application of USP 5,908,858).

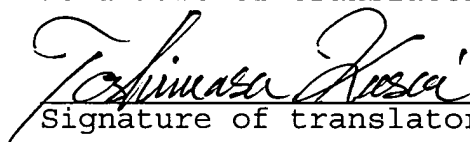
I state that I compared the attached translation of said priority document with said Japanese language priority document and that said attached translation is accurate.

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May 17, 2001

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English Translation
of Certified Copy

Patent Office
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This is to certify that the annexed is a true copy of the following application as
filed with this Office.

Date of Application : April 5, 1996

Application Number : Patent Application No. Hei 08-083562

Applicant(s) : SANKYO COMPANY, LIMITED

Date : February 21, 1997

Commissioner, Hisamitsu Arai
Patent Office

Official Seal
Certificate Serial Hei No. 09-3007

08-083562

| | |
|-------------------------------------|--|
| Name of Document | Patent Application |
| Docket Number | 96002SM |
| Filing Date | April 5, 1996 |
| Address to | Commissioner, Patent Office |
| International Patent Classification | C07D207/00 |
| Title of Invention | 1,2-Diphenylpyrrole derivatives and pharmaceutical compositions thereof |
| Number of Claim | 16 |
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Indication of Official Fee

| | |
|----------------------------|------------|
| Means for Payment | |
| Prepayment Register Number | 010216 |
| Amount to be Paid | 21,000 yen |

List of Materials to be submitted

| | | |
|-------------------------------------|---------------|---------|
| Name of Material | Specification | 1 |
| Name of Material | Abstract | 1 |
| Number of General Power of Attorney | | 9001823 |
| Number of General Power of Attorney | | 9001821 |
| Number of General Power of Attorney | | 9001822 |

Necessity for Proof

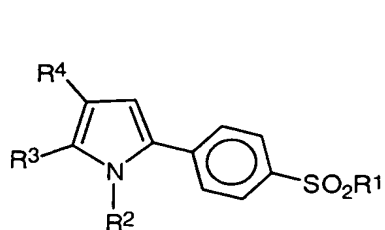
Yes

[Document name] Abstract

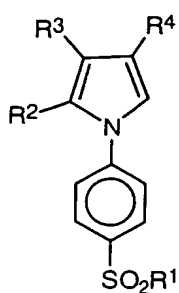
[Abstract]

- 5 [Problem] To provide analgesics, anti-inflammatory agents and/or antipyretics having selective inhibiting effect on a cyclooxygenase-2 and/or suppressing effect on the production of inflammatory cytokinins.

[Solution] 1,2-Diphenylpyrrole derivatives having formulae (I) and (II):



(I)



(II)

10

15

(wherein R¹ represents a methyl group or an amino group; R² represents an unsubstituted or substituted phenyl group; R³ represents a hydrogen atom, a halogen atom, a lower alkyl group or a halogenated lower alkyl group; and R⁴ represents a hydrogen atom, an unsubstituted or substituted alkyl group, a cycloalkyl group, an unsubstituted or substituted aryl group or an unsubstituted or substituted aralkyl group.

[Selected drawing] None

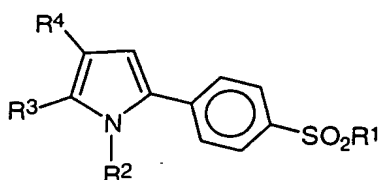
[Document name] Specification

[Title of the invention] 1,2-Diphenylpyrrole derivatives and pharmaceutical compositions thereof

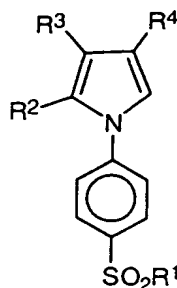
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[Scope of Claim for Patent]

[Claim 1] Compounds of formula (I) and (II), or pharmaceutically acceptable salts thereof:



(I)



(II)

10 [wherein:

R¹ represents a lower alkyl group or an amino group,

15 R² represents a phenyl group or a phenyl group substituted by at least one substituent selected from the group consisting of <Substituents A> and <SubstituentsB>;

20 R³ represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted by at least one substituent selected from the group consisting of <Substituents A>;

R⁴ represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted by at least one substituent selected from the group consisting of <Substituents A>, a cycloalkyl group, an aryl group, an aryl group substituted by at least one substituent selected from the group consisting of <Substituents A> and <SubstituentsB>, an aralkyl group or an aralkyl group substituted by at least one substituent selected from the group consisting of <Substituents A> and <SubstituentsB>]

<Substituents A>

hydroxy groups, halogen atoms, lower alkoxy groups and lower alkylthio groups.

5 <Substituents B>

lower alkyl groups, lower alkyl groups which are substituted by at least one substituent selected from the group consisting of <Substituents A>, cycloalkyloxy groups, halogenated lower alkoxy groups and lower alkylenedioxy groups.

10 [Claim 2] The compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein R¹ represents a methyl group or an amino group.

[Claim 3] The compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein R¹ represents an amino group.

15

[Claim 4] The compounds of any one claim selected from Claims 1 to 3, or pharmaceutically acceptable salts thereof, wherein R² represents a phenyl group or a phenyl group substituted by at least one substituent selected from the group consisting of <Substituents A¹> and <Substituents B¹>.

20

<Substituents A¹>

halogen atoms, lower alkoxy groups and lower alkylthio groups.

<Substituents B¹>

25 lower alkyl groups, lower alkyl groups which are substituted by at least one substituent selected from the group consisting of <Substituents A¹>, halogenated lower alkoxy groups and lower alkylenedioxy groups.

30 [Claim 5] The compounds of Claim 4 or pharmaceutically acceptable salts thereof, wherein R² represents a phenyl group or a phenyl group substituted by at least one substituent selected from the group consisting of <Substituents A¹> and <Substituents B²>.

<Substituents A¹>

halogen atoms, lower alkoxy groups and lower alkylthio groups.

<Substituents B²>

5 lower alkyl groups, halogenated lower alkyl groups, halogenated lower alkoxy groups and lower alkylenedioxy groups.

[Claim 6] The compounds of Claim 4 or pharmaceutically acceptable salts thereof, wherein R² represents a phenyl group or a phenyl group substituted by from 1 to 3 of substituents
10 selected from the group consisting of <Substituents A¹> and <Substituents B¹>.

[Claim 7] The compounds of any one claim selected from Claims 1 to 6, or pharmaceutically acceptable salts thereof, wherein R³ represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted by at least one substituent selected from the
15 group consisting of <Substituents A¹>.

<Substituents A¹>

halogen atoms, lower alkoxy groups and lower alkylthio groups.

20 [Claim 8] The compounds of Claim 7 or pharmaceutically acceptable salts thereof, wherein R³ represents a hydrogen atom, a halogen atom, a lower alkyl group or a halogenated lower alkyl group.

[Claim 9] The compounds of any one claim selected from Claims 1 to 8, or pharmaceutically
25 acceptable salts thereof, wherein R⁴ represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted by at least one substituent selected from the group consisting of <Substituents A>, a cycloalkyl group, an aryl group, an aryl group substituted by at least one substituent selected from the group consisting of <Substituents A¹> and <Substituents B³>, an aralkyl group or an aralkyl group substituted by at least one substituent selected from the
30 group consisting of <Substituents A¹> and <Substituents B³>.

<Substituents A¹>

halogen atoms, lower alkoxy groups and lower alkylthio groups.

<Substituents B³>

lower alkyl groups, lower alkyl groups which are substituted by at least one substituent
5 selected from the group consisting of <Substituents A> and cycloalkyloxy groups.

[Claim 10] The compounds of Claim 9 or pharmaceutically acceptable salts thereof, wherein
R⁴ represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted by at
least one substituent selected from the group consisting of <Substituents A²>, a cycloalkyl
10 group, an aryl group, an aryl group substituted by at least one substituent selected from the
group consisting of <Substituents A²> and <Substituents B³>, an aralkyl group or an aralkyl
group substituted by at least one substituent selected from the group consisting of
<Substituents A²> and <Substituents B³>.

15 <Substituents A²>

hydroxy groups, halogen atoms and lower alkoxy groups.

<Substituents B³>

lower alkyl groups, halogenated lower alkyl groups and cycloalkyloxy groups.
20

[Claim 11] The compound of Claim 1, which is selected from the group consisting of:

3-methyl-2-(4-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole,
4-methyl-2-(4-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole,
1-(4-fluorophenyl)-2-(4-sulfamoylphenyl)pyrrole,
25 1-(4-fluorophenyl)-4-methyl-2-(4-sulfamoylphenyl)pyrrole,
5-fluoro-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole,
2-(4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole,
1-(4-methoxyphenyl)-4-methyl-2-(4-sulfamoylphenyl)pyrrole,
4-ethyl-2-(4-methoxyphenyl)-1-(4-sulfamoylphenyl)pyrrole,
30 2-(4-chlorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole,
4-methyl-2-(4-methylthiophenyl)-1-(4-sulfamoylphenyl)pyrrole,
2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole,

4-methyl-2-(4-methoxy-3-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole,
2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole,
4-methyl-2-phenyl-1-(4-sulfamoylphenyl)pyrrole,
4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl)pyrrole, and
5 2-(3-chloro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole;
or pharmaceutically acceptable salts thereof

[Claim 12] A cyclooxygenase-2 selective inhibitor containing as an active ingredient the
compound of any one claim selected from Claims 1 to 11 or pharmaceutically acceptable
10 salts thereof.

[Claim 13] An inhibitor against inflammatory cytokine production containing as an active
ingredient the compound of any one claim selected from Claims 1 to 11 or pharmaceutically
acceptable salts thereof.

15 [Claim 14] An analgesic agent containing as an active ingredient the compound of any one
claim selected from Claims 1 to 11 or pharmaceutically acceptable salts thereof.

[Claim 15] An anti-inflammatory agent containing as an active ingredient the compound of
20 any one claim selected from Claims 1 to 11 or pharmaceutically acceptable salts thereof.

[Claim 16] An antipyretic agent containing as an active ingredient the compound of any one
claim selected from Claims 1 to 11 or pharmaceutically acceptable salts thereof.

25 [Detailed description of the invention]

[Technical field to which the invention belongs]

The present invention relates to a series of new 1,2-diphenylpyrrole derivatives and
compositions using these novel compounds, which have valuable analgesic, anti-
inflammatory, anti-pyretic and anti-allergic activities having particularly excellent selective
30 inhibiting effect on a cyclooxygenase-2 and suppressing effect on the production of
inflammatory cytokines.

[Prior arts]

Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used for clinical purposes for the treatment of inflammatory diseases, such as pyrexia, pain and edema. However, the adverse effects of these drugs, such as gastrointestinal disorders and renal disorders, present problems to any patient who takes the drug for an extended period of time as well as to older patients.

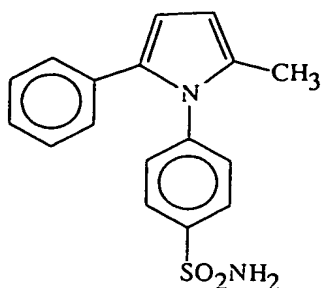
It has recently been found that two isozymes, called COX-1 and COX-2, are present in COX at which these NSAIDs act.

It has been discovered that COX-1 is normally present in the stomach, the intestines, the kidneys and other tissues and serves to produce PG which functions physiologically, while COX-2 is induced by inflammatory cytokines and endotoxins, such as IL-1, TNF α , and the like, and is expressed specifically at an inflammatory site to produce PG which functions as a mediator of inflammatory reactions. With the discovery of these two isozymes, it was thought that anti-inflammatory agents which specifically inhibit COX-2 without inhibiting COX-1 would be free from the side effects caused by conventional drugs and could be a new type of anti-inflammatory agent.

On the other hand, it is known that IL-1, TNF α , IL-6 and IL-8, the inflammatory cytokines, are produced in monocytes, macrophages and synovial cells as a result of various inflammatory stimulants and influence a number of biological processes, such as the production of PG, the expression of cell adhesion molecules, the production of collagenase-protease, the activation of osteoclasts, pyrexia, the production of acute phase protein, and chemotactic activity of leukocytes.

It is said that these cytokines are associated with the progression of various diseases, such as the chronic inflammatory diseases, including chronic rheumatic arthritis. Thus, drugs which inhibit cytokine actions are useful as a new type of anti-inflammatory agent.

Amongst the known 1,2-diphenylpyrrole derivatives having analgesic and antiphlogistic actions, a compound represented by the following formula is disclosed in German Patent No. 1938904:



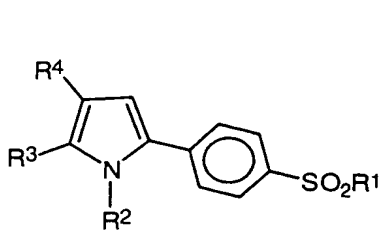
However, this compound is not sufficiently effective, and so more effective compounds would be desirable.

[Problem to be solved by the invention]

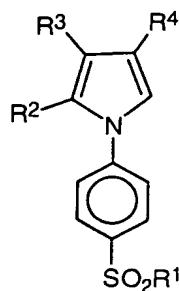
5 The present inventors made intensive studies for years on the synthesis of pyrrole derivatives which inhibit selectively a cyclooxygenase-2 that is the important inflammatory factor described above, and inhibit the production of the inflammatory cytokines, particularly IL-1 and TNF α , and on their pharmacological activities. As the result, we found that 1,2-diphenylpyrrole derivatives (I) and (II) have excellent selective inhibiting effect on a
10 cyclooxygenase-2 action and/or inhibiting effect on the production of inflammatory cytokines.

[Means for solving the problem]

The 1,2-diphenylpyrrole derivatives of the present invention are those compounds of formula (I) and (II):



(I)



(II)

[wherein:

R¹ represents a lower alkyl group or an amino group,

R² represents a phenyl group or a phenyl group substituted by at least one substituent selected from the group consisting of <Substituents A> and <Substituents B>;

R³ represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted by at least one substituent selected from the group consisting of <Substituents A>;

5 R⁴ represents a hydrogen atom, a lower alkyl group, a lower alkyl group substituted by at least one substituent selected from the group consisting of <Substituents A>, a cycloalkyl group, an aryl group, an aryl group substituted by at least one substituent selected from the group consisting of <Substituents A> and <Substituents B>, an aralkyl group or an aralkyl group substituted by at least one substituent selected from the group consisting of <Substituents A> and <Substituents B>;]
10 or pharmaceutically acceptable salts thereof:

<Substituents A>

hydroxy groups, halogen atoms, lower alkoxy groups and lower alkylthio groups.

<Substituents B>

15 lower alkyl groups, lower alkyl groups which are substituted by at least one substituent selected from the group consisting of <Substituents A>, cycloalkyloxy groups, halogenated lower alkoxy groups and lower alkylenedioxy groups.

In the formula (I) and (II), R¹ is preferably a methyl group or an amino group, and is particularly preferably an amino group.

20 In the formula (I) and (II), R² is preferably a phenyl group or a phenyl group substituted by at least one substituent selected from the group consisting of <Substituents A¹> and <Substituents B¹>.

<Substituents A¹>

halogen atoms, lower alkoxy groups and lower alkylthio groups.

<Substituents B¹>

25 lower alkyl groups, lower alkyl groups which are substituted by at least one substituent selected from the group consisting of <Substituents A¹>, halogenated lower alkoxy groups and lower alkylenedioxy groups.

R² is particularly preferably a phenyl group or a phenyl group substituted by at least one substituent selected from the group consisting of <Substituents A¹> and <Substituents B²>.

30 <Substituents A¹>

halogen atoms, lower alkoxy groups and lower alkylthio groups.

<Substituents B²>

lower alkyl groups, halogenated lower alkyl groups, halogenated lower alkoxy groups and lower alkylenedioxy groups.

5 R² is most preferably a phenyl group or a phenyl group substituted by from 1 to 3 of substituents selected from the group consisting of <Substituents A¹> and <Substituents B¹>.

10 Substituents of the substituted phenyl group in R² include halogen atoms such as fluorine, chlorine, bromine and iodine; C₁-C₄ alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl and t-butyl; halogeno C₁-C₄ alkyl groups such as fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, 4-fluorobutyl, chloromethyl, trichloromethyl and bromomethyl; C₁-C₄ alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, s-butoxy and t-butoxy; C₁-C₄ alkylthio groups such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, s-butylthio and t-butylthio; halogeno C₁-C₄ alkoxy groups such as fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 3-fluoropropoxy, 4-fluorobutoxy, 2-chloroethoxy and 2-bromoethoxy; and C₁-C₄ alkylenedioxy groups such as methylenedioxy and ethylenedioxy.

20 Specific examples of R² preferably include phenyl groups, phenyl groups having 1 to 3 substituents selected from the groups consisting of halogen atoms, C₁-C₄ alkyl groups, C₁-C₄ alkoxy groups and C₁-C₄ alkylthio groups such as 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, p-tolyl, 4-ethylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-methylthiophenyl, 4-ethylthiophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,4-dichlorophenyl, 2,4-dichlorophenyl, 3,4-dimethylphenyl, 3,4-dimethoxyphenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3,5-dichloro-4-methoxyphenyl and 4-methoxy-3,5-dimethylphenyl; phenyl groups substituted by trifluoromethyl, difluoromethoxy or trifluoromethoxy such as 4-trifluoromethylphenyl, 4-difluoromethoxyphenyl and 4-trifluoromethoxyphenyl; phenyl groups substituted by methylenedioxy or ethylenedioxy such as 3,4-methylenedioxyphenyl and 3,4-ethylenedioxyphenyl.

30 In the formula (I) and (II), R³ is preferably a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkyl group substituted by at least one substituent selected from the group consisting of <Substituents A¹>.

<Substituents A¹>

halogen atoms, lower alkoxy groups and lower alkylthio groups.

R³ is particularly preferably a hydrogen atom, a halogen atom, a lower alkyl group or a halogenated lower alkyl group.

5 R³ includes a hydrogen atom; a halogen atom such as fluorine, chlorine, bromine and iodine; a C₁-C₄ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl and t-butyl; or a halogeno C₁-C₄ alkyl group such as fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, 4-fluorobutyl, 2-chloroethyl and 3-chloropropyl.

10 R³ is preferably a hydrogen atom; a halogen atom such as fluorine, chlorine, bromine and iodine; a methyl group, an ethyl group, a fluoromethyl group, a difluoromethyl group, a 2-fluoroethyl group or a 2-chloroethyl group.

In the formula (I) and (II), R⁴ is preferably a hydrogen atom, a lower alkyl group, a lower alkyl group substituted by at least one substituent selected from the group consisting of
15 <Substituents A>, a cycloalkyl group, an aryl group, an aryl group substituted by at least one substituent selected from the group consisting of <Substituents A¹> and <Substituents B³>, an aralkyl group or an aralkyl group substituted by at least one substituent selected from the group consisting of <Substituents A¹> and <Substituents B³>.

<Substituents A¹>

20 halogen atoms, lower alkoxy groups and lower alkylthio groups.

<Substituents B³>

lower alkyl groups, lower alkyl groups which are substituted by at least one substituent selected from the group consisting of <Substituents A> and cycloalkyloxy groups.

R⁴ is particularly preferably a hydrogen atom, a lower alkyl group, a lower alkyl group substituted by at least one substituent selected from the group consisting of <Substituents
25 A²>, a cycloalkyl group, an aryl group, an aryl group substituted by at least one substituent selected from the group consisting of <Substituents A²> and <Substituents B³>, an aralkyl group or an aralkyl group substituted by at least one substituent selected from the group consisting of <Substituents A²> and <Substituents B³>.

30 <Substituents A²>

hydroxy groups, halogen atoms and lower alkoxy groups.

<Substituents B³>

lower alkyl groups, halogenated lower alkyl groups and cycloalkyloxy groups.

R⁴ includes a hydrogen atom; a C₁-C₆ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl and hexyl; an alkyl group as defined above which has substituents selected from the groups consisting of hydroxy groups; halogen atoms
5 such as fluorine, chlorine, bromine and iodine; and C₁-C₄ alkoxy groups such as methoxy, —> ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, s-butoxy and t-butoxy; a C₃-C₇ cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; a C₆-C₁₀ aryl group such as phenyl and naphthyl, which may has the substituents as difined below; and a C₆-C₁₀ aryl C₁-C₄ alkyl group which may has the substituents as defined below in the aryl
10 part such as benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 1-naphthylmethyl and 2-naphthylmethyl.

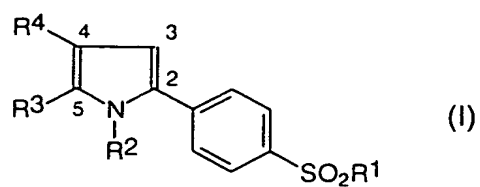
Substituents of the aryl group or the aryl part of the arylalkyl group, as defined above, include halogen atoms such as fluorine, chlorine, bromine and iodine; C₁-C₄ alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl and t-butyl; halogeno C₁-C₄
15 alkyl groups such as fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, trichloromethyl, chlorodifluoromethyl, 2-fluoromethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 3-fluoropropyl and 4-fluoropropyl; C₁-C₄ alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, s-butoxy and t-butoxy; and C₃-C₇ cycloalkyloxy groups such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and
20 cycloheptyloxy.

R⁴ preferably includes a hydrogen atom; a C₁-C₄ alkyl group such as methyl, ethyl, isopropyl, butyl and isobutyl; a mono-, di- or tri-halogeno C₁-C₄ alkyl group such as fluoromethyl, difluoromethyl, chlorodifluoromethyl, bromodifluoromethyl, trifluoromethyl, 2-fluoroethyl and 2,2,2-trifluoroethyl; a hydroxymethyl group; a C₁-C₄ alkoxymethyl group
25 such as methoxymethyl and ethoxymethyl; a C₃-C₆ cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; a phenyl group; a mono- or di-fluorophenyl group such as 4-fluorophenyl and 2,4-difluorophenyl; a mono- or di-methoxyphenyl group such as 4-methoxyphenyl and 3,4-dimethoxyphenyl; a tolyl group such as p-tolyl and o-tolyl; a cyclopentyloxy(methoxy)phenyl group such as 3-cyclopentyloxy-4-methoxyphenyl; a
30 trifluoromethylphenyl group such as 4-trifluoromethylphenyl; a benzyl group; a substituted benzyl group such as 4-methoxybenzyl and 3-cyclopentyloxy-4-methoxybenzyl; a phenethyl

group; a naphthyl group such as 1-naphthyl and 2-naphthyl; and a naphthylmethyl group such as 1-naphthylmethyl and 2-naphthylmethyl.

5 Representative compounds of 1,2-diphenylpyrrole derivatives having the formula (I) and (II) of the present invention are illustrated in Tables 1 and 2. In Table 1 and Table 2, the compounds wherein R^3 is mainly a hydrogen atom are illustrated, and further the corresponding compounds wherein R^3 is fluoro, chloro, bromo, iodo or methyl are also preferable compounds.

Table 1



| No. | R ¹ | R ² | R ³ | R ⁴ |
|-----|----------------|----------------|-------------------|----------------|
| 1 | Me | Ph | H | H |
| 2 | Me | Ph | H | Me |
| 3 | Me | 4-F-Ph | H | H |
| 4 | Me | 4-F-Ph | F | H |
| 5 | Me | 4-F-Ph | Cl | H |
| 6 | Me | 4-F-Ph | Br | H |
| 7 | Me | 4-F-Ph | I | H |
| 8 | Me | 4-F-Ph | Me | H |
| 9 | Me | 4-F-Ph | Et | H |
| 10 | Me | 4-F-Ph | Pr | H |
| 11 | Me | 4-F-Ph | Bu | H |
| 12 | Me | 4-F-Ph | CH ₂ F | H |
| 13 | Me | 4-F-Ph | CHF ₂ | H |
| 14 | Me | 4-F-Ph | CF ₃ | H |
| 15 | Me | 4-F-Ph | H | Me |
| 16 | Me | 4-F-Ph | F | Me |
| 17 | Me | 4-F-Ph | Cl | Me |
| 18 | Me | 4-F-Ph | Br | Me |
| 19 | Me | 4-F-Ph | I | Me |
| 20 | Me | 4-F-Ph | Me | Me |
| 21 | Me | 4-F-Ph | Et | Me |
| 22 | Me | 4-F-Ph | Pr | Me |
| 23 | Me | 4-F-Ph | H | Et |

Table 1 (cont.)

| No. | R ¹ | R ² | R ³ | R ⁴ |
|-----|----------------|------------------------|----------------|--------------------|
| 24 | Me | 4-F-Ph | H | Pr |
| 25 | Me | 4-F-Ph | H | Bu |
| 26 | Me | 4-F-Ph | H | c-Pr |
| 27 | Me | 4-F-Ph | H | Ph |
| 28 | Me | 4-F-Ph | H | CH ₂ Ph |
| 29 | Me | 4-F-Ph | H | CHF ₂ |
| 30 | Me | 4-F-Ph | Me | CHF ₂ |
| 31 | Me | 4-F-Ph | H | CF ₃ |
| 32 | Me | 4-F-Ph | Me | CF ₃ |
| 33 | Me | 4-MeO-Ph | H | H |
| 34 | Me | 4-MeO-Ph | H | Me |
| 35 | Me | 4-Cl-Ph | H | H |
| 36 | Me | 4-Cl-Ph | H | Me |
| 37 | Me | 4-Me-Ph | H | H |
| 38 | Me | 4-Me-Ph | H | Me |
| 39 | Me | 3-Cl-4-F-Ph | H | H |
| 40 | Me | 3-Cl-4-F-Ph | H | Me |
| 41 | Me | 3,4-methylenedioxy-Ph | H | H |
| 42 | Me | 3,4-methylenedioxy-Ph | H | Me |
| 43 | Me | 3-Cl-4-MeO-Ph | H | H |
| 44 | Me | 3-Cl-4-MeO-Ph | H | Me |
| 45 | Me | 4-CF ₃ -Ph | H | H |
| 46 | Me | 4-CF ₃ O-Ph | H | H |
| 47 | Me | 3-F-4-MeO-Ph | H | H |
| 48 | Me | 3-F-4-MeO-Ph | H | Me |
| 49 | Me | 3-Me-4-MeO-Ph | H | H |
| 50 | Me | 3-Me-4-MeO-Ph | H | Me |
| 51 | Me | 3,4-diF-Ph | H | H |
| 52 | Me | 3,4-diF-Ph | H | Me |

Table 1 (cont.)

| No. | R ¹ | R ² | R ³ | R ⁴ |
|-----|-----------------|----------------|----------------|---------------------|
| 53 | Me | 2,4-diF-Ph | H | H |
| 54 | Me | 2,4-diF-Ph | H | Me |
| 55 | Me | 3,4-diMe-Ph | H | H |
| 56 | Me | 3,4-diMe-Ph | H | Me |
| 57 | Me | 3,4-diCl-Ph | H | H |
| 58 | Me | 3,4-diCl-Ph | H | Me |
| 59 | Me | 3,4-di(MeO)-Ph | H | H |
| 60 | Me | 3,4-di(MeO)-Ph | H | Me |
| 61 | Me | 4-F-Ph | H | CH ₂ OH |
| 62 | Me | 4-F-Ph | Me | CH ₂ OH |
| 63 | Me | 4-F-Ph | H | CH ₂ OMe |
| 64 | Me | 4-MeO-Ph | H | CH ₂ OH |
| 65 | Me | 4-MeO-Ph | H | CH ₂ OMe |
| 66 | Me | 4-Cl-Ph | H | CH ₂ OH |
| 67 | Me | 4-Cl-Ph | H | CH ₂ OMe |
| 68 | Me | 4-Me-Ph | H | CH ₂ OH |
| 69 | Me | 4-Me-Ph | H | CH ₂ OMe |
| 70 | NH ₂ | Ph | H | H |
| 71 | NH ₂ | Ph | H | Me |
| 72 | NH ₂ | Ph | Me | H |
| 73 | NH ₂ | 4-F-Ph | H | H |
| 74 | NH ₂ | 4-F-Ph | H | Me |
| 75 | NH ₂ | 4-F-Ph | Cl | Me |
| 76 | NH ₂ | 4-F-Ph | Me | H |
| 77 | NH ₂ | 4-F-Ph | H | Et |
| 78 | NH ₂ | 4-F-Ph | H | Pr |
| 79 | NH ₂ | 4-F-Ph | H | Bu |
| 80 | NH ₂ | 4-F-Ph | H | c-Pr |

Table 1 (cont.)

| No. | R ¹ | R ² | R ³ | R ⁴ |
|-----|-----------------|-----------------------|----------------|--------------------|
| 81 | NH ₂ | 4-F-Ph | H | Ph |
| 82 | NH ₂ | 4-F-Ph | H | CH ₂ Ph |
| 83 | NH ₂ | 4-F-Ph | H | CHF ₂ |
| 84 | NH ₂ | 4-F-Ph | H | CF ₃ |
| 85 | NH ₂ | 4-MeO-Ph | H | H |
| 86 | NH ₂ | 4-MeO-Ph | H | Me |
| 87 | NH ₂ | 4-MeO-Ph | H | Bu |
| 88 | NH ₂ | 4-MeO-Ph | Me | H |
| 89 | NH ₂ | 4-EtO-Ph | H | H |
| 90 | NH ₂ | 4-EtO-Ph | H | Me |
| 91 | NH ₂ | 4-EtO-Ph | Me | H |
| 92 | NH ₂ | 4-PrO-Ph | H | Me |
| 93 | NH ₂ | 4-MeS-Ph | H | H |
| 94 | NH ₂ | 4-MeS-Ph | H | Me |
| 95 | NH ₂ | 4-MeS-Ph | Me | H |
| 96 | NH ₂ | 4-Cl-Ph | H | H |
| 97 | NH ₂ | 4-Cl-Ph | H | Me |
| 98 | NH ₂ | 4-Cl-Ph | Me | H |
| 99 | NH ₂ | 4-Me-Ph | H | H |
| 100 | NH ₂ | 4-Me-Ph | H | Me |
| 101 | NH ₂ | 4-Me-Ph | Me | H |
| 102 | NH ₂ | 3-Cl-4-F-Ph | H | H |
| 103 | NH ₂ | 3-Cl-4-F-Ph | H | Me |
| 104 | NH ₂ | 3-Cl-4-F-Ph | Me | H |
| 105 | NH ₂ | 3,4-methylenedioxy-Ph | H | H |
| 106 | NH ₂ | 3,4-methylenedioxy-Ph | H | Me |
| 107 | NH ₂ | 3-Cl-4-MeO-Ph | H | H |
| 108 | NH ₂ | 3-Cl-4-MeO-Ph | H | Me |
| 109 | NH ₂ | 3-Cl-4-MeO-Ph | Me | H |

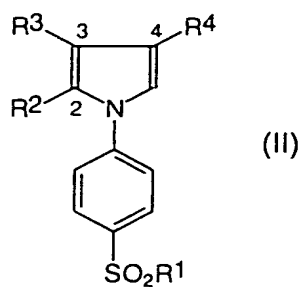
Table 1 (cont.)

| No. | R ¹ | R ² | R ³ | R ⁴ |
|-----|-----------------|------------------------|----------------|---------------------|
| 110 | NH ₂ | 4-CF ₃ -Ph | H | H |
| 111 | NH ₂ | 4-CF ₃ O-Ph | H | H |
| 112 | NH ₂ | 3-F-4-MeO-Ph | H | H |
| 113 | NH ₂ | 3-F-4-MeO-Ph | H | Me |
| 114 | NH ₂ | 3-F-4-MeO-Ph | Me | H |
| 115 | NH ₂ | 3-Me-4-MeO-Ph | H | H |
| 116 | NH ₂ | 3-Me-4-MeO-Ph | H | Me |
| 117 | NH ₂ | 3-Me-4-MeO-Ph | Me | H |
| 118 | NH ₂ | 3,4-diF-Ph | H | H |
| 119 | NH ₂ | 3,4-diF-Ph | H | Me |
| 120 | NH ₂ | 3,4-diF-Ph | Me | H |
| 121 | NH ₂ | 2,4-diF-Ph | H | H |
| 122 | NH ₂ | 2,4-diF-Ph | H | Me |
| 123 | NH ₂ | 2,4-diF-Ph | Me | H |
| 124 | NH ₂ | 3,4-diMe-Ph | H | H |
| 125 | NH ₂ | 3,4-diMe-Ph | H | Me |
| 126 | NH ₂ | 3,4-diMe-Ph | Me | H |
| 127 | NH ₂ | 2,4-diCl-Ph | H | H |
| 128 | NH ₂ | 2,4-diCl-Ph | H | Me |
| 129 | NH ₂ | 2,4-diCl-Ph | Me | H |
| 130 | NH ₂ | 3,4-diCl-Ph | H | H |
| 131 | NH ₂ | 3,4-diCl-Ph | H | Me |
| 132 | NH ₂ | 3,4-diCl-Ph | Me | H |
| 133 | NH ₂ | 3,4-di(MeO)-Ph | H | H |
| 134 | NH ₂ | 3,4-di(MeO)-Ph | H | Me |
| 135 | NH ₂ | 4-F-Ph | H | CH ₂ OH |
| 136 | NH ₂ | 4-F-Ph | H | CH ₂ OMe |
| 137 | NH ₂ | 4-MeO-Ph | H | CH ₂ OH |
| 138 | NH ₂ | 4-MeO-Ph | H | CH ₂ OMe |

Table 1 (cont.)

| No. | R ¹ | R ² | R ³ | R ⁴ |
|-----|-----------------|----------------|----------------|---------------------|
| 139 | NH ₂ | 4-Cl-Ph | H | CH ₂ OH |
| 140 | NH ₂ | 4-Cl-Ph | H | CH ₂ OMe |
| 141 | NH ₂ | 4-Me-Ph | H | CH ₂ OH |
| 142 | NH ₂ | 4-Me-Ph | H | CH ₂ OMe |
| 143 | NH ₂ | 4-Et-Ph | H | H |
| 144 | NH ₂ | 4-Et-Ph | H | Me |
| 145 | NH ₂ | 4-Et-Ph | Me | H |

Table 2



| No. | R ¹ | R ² | R ³ | R ⁴ |
|-----|----------------|----------------|----------------|--------------------|
| 1 | Me | Ph | H | H |
| 2 | Me | Ph | H | Me |
| 3 | Me | 4-F-Ph | H | H |
| 4 | Me | 4-F-Ph | F | H |
| 5 | Me | 4-F-Ph | Cl | H |
| 6 | Me | 4-F-Ph | Br | H |
| 7 | Me | 4-F-Ph | I | H |
| 8 | Me | 4-F-Ph | Me | H |
| 9 | Me | 4-F-Ph | Et | H |
| 10 | Me | 4-F-Ph | Pr | H |
| 11 | Me | 4-F-Ph | H | Me |
| 12 | Me | 4-F-Ph | H | Et |
| 13 | Me | 4-F-Ph | H | Pr |
| 14 | Me | 4-F-Ph | H | Bu |
| 15 | Me | 4-F-Ph | H | c-Pr |
| 16 | Me | 4-F-Ph | H | Ph |
| 17 | Me | 4-F-Ph | H | CH ₂ Ph |
| 18 | Me | 4-F-Ph | H | CHF ₂ |
| 19 | Me | 4-F-Ph | H | CF ₃ |
| 20 | Me | 4-MeO-Ph | H | H |
| 21 | Me | 4-MeO-Ph | Me | H |
| 22 | Me | 4-MeO-Ph | H | Me |
| 23 | Me | 4-Cl-Ph | H | H |

Table 2 (cont.)

| No. | R ¹ | R ² | R ³ | R ⁴ |
|-----|----------------|-------------------------|----------------|---------------------|
| 24 | Me | 4-Cl-Ph | Me | H |
| 25 | Me | 4-Me-Ph | H | H |
| 26 | Me | 4-Me-Ph | Me | H |
| 27 | Me | 4-Me-Ph | H | Me |
| 28 | Me | 3-Cl-4-F-Ph | H | H |
| 29 | Me | 3-Cl-4-F-Ph | H | Me |
| 30 | Me | 3,4-methylenedioxy-Ph | H | H |
| 31 | Me | 3,4-methylenedioxy-Ph | H | Me |
| 32 | Me | 3-Cl-4-MeO-Ph | H | H |
| 33 | Me | 3-Cl-4-MeO-Ph | H | Me |
| 34 | Me | 4-CF ₃ -Ph | H | H |
| 35 | Me | 4-CF ₃ O-Ph | H | H |
| 36 | Me | 4-CHF ₂ O-Ph | H | H |
| 37 | Me | 4-CHF ₂ O-Ph | Me | H |
| 38 | Me | 3-F-4-MeO-Ph | H | H |
| 39 | Me | 3-F-4-MeO-Ph | H | Me |
| 40 | Me | 3-Me-4-MeO-Ph | H | H |
| 41 | Me | 3-Me-4-MeO-Ph | H | Me |
| 42 | Me | 3,4-diF-Ph | H | H |
| 43 | Me | 3,4-diF-Ph | H | Me |
| 44 | Me | 2,4-diF-Ph | H | H |
| 45 | Me | 2,4-diF-Ph | H | Me |
| 46 | Me | 3,4-diMe-Ph | H | H |
| 47 | Me | 3,4-diCl-Ph | H | H |
| 48 | Me | 3,4-diCl-Ph | H | Me |
| 49 | Me | 3,4-di(MeO)-Ph | H | H |
| 50 | Me | 3,4-di(MeO)-Ph | H | Me |
| 51 | Me | 4-F-Ph | H | CH ₂ OH |
| 52 | Me | 4-F-Ph | H | CH ₂ OMe |

Table 2 (cont.)

| No. | R ¹ | R ² | R ³ | R ⁴ |
|-----|-----------------|----------------|----------------|---------------------|
| 53 | Me | 4-MeO-Ph | H | CH ₂ OH |
| 54 | Me | 4-MeO-Ph | H | CH ₂ OMe |
| 55 | Me | 4-Cl-Ph | H | CH ₂ OH |
| 56 | Me | 4-Cl-Ph | H | CH ₂ OMe |
| 57 | Me | 4-Me-Ph | H | CH ₂ OH |
| 58 | Me | 4-Me-Ph | H | CH ₂ OMe |
| 59 | NH ₂ | Ph | H | H |
| 60 | NH ₂ | Ph | H | Me |
| 61 | NH ₂ | Ph | Me | H |
| 62 | NH ₂ | 4-F-Ph | H | H |
| 63 | NH ₂ | 4-F-Ph | H | Me |
| 64 | NH ₂ | 4-F-Ph | Me | H |
| 65 | NH ₂ | 4-F-Ph | H | Et |
| 66 | NH ₂ | 4-F-Ph | H | Pr |
| 67 | NH ₂ | 4-F-Ph | H | Bu |
| 68 | NH ₂ | 4-F-Ph | H | c-Pr |
| 69 | NH ₂ | 4-F-Ph | H | Ph |
| 70 | NH ₂ | 4-F-Ph | H | CH ₂ Ph |
| 71 | NH ₂ | 4-F-Ph | H | CHF ₂ |
| 72 | NH ₂ | 4-F-Ph | H | CF ₃ |
| 73 | NH ₂ | 4-MeO-Ph | H | H |
| 74 | NH ₂ | 4-MeO-Ph | H | Me |
| 75 | NH ₂ | 4-MeO-Ph | H | Et |
| 76 | NH ₂ | 4-MeO-Ph | Me | H |
| 77 | NH ₂ | 4-EtO-Ph | H | H |
| 78 | NH ₂ | 4-EtO-Ph | H | Me |
| 79 | NH ₂ | 4-EtO-Ph | Me | H |
| 80 | NH ₂ | 4-PrO-Ph | H | Me |

Table 2 (cont.)

| No. | R ¹ | R ² | R ³ | R ⁴ |
|-----|-----------------|-------------------------|----------------|----------------|
| 81 | NH ₂ | 4-MeS-Ph | H | H |
| 82 | NH ₂ | 4-MeS-Ph | H | Me |
| 83 | NH ₂ | 4-MeS-Ph | Me | H |
| 84 | NH ₂ | 4-Cl-Ph | H | H |
| 85 | NH ₂ | 4-Cl-Ph | H | Me |
| 86 | NH ₂ | 4-Cl-Ph | Me | H |
| 87 | NH ₂ | 4-Me-Ph | H | H |
| 88 | NH ₂ | 4-Me-Ph | Me | H |
| 89 | NH ₂ | 4-Me-Ph | H | Me |
| 90 | NH ₂ | 4-Et-Ph | H | H |
| 91 | NH ₂ | 4-Et-Ph | H | Me |
| 92 | NH ₂ | 4-Et-Ph | Me | H |
| 93 | NH ₂ | 4-i-Pr-Ph | H | Me |
| 94 | NH ₂ | 3-Cl-4-F-Ph | H | H |
| 95 | NH ₂ | 3-Cl-4-F-Ph | H | Me |
| 96 | NH ₂ | 3-Cl-4-F-Ph | Me | H |
| 97 | NH ₂ | 3,4-methylenedioxy-Ph | H | H |
| 98 | NH ₂ | 3,4-methylenedioxy-Ph | H | Me |
| 99 | NH ₂ | 3-Cl-4-MeO-Ph | H | H |
| 100 | NH ₂ | 3-Cl-4-MeO-Ph | H | Me |
| 101 | NH ₂ | 3-Cl-4-MeO-Ph | Me | H |
| 102 | NH ₂ | 4-CF ₃ -Ph | H | Me |
| 103 | NH ₂ | 4-CHF ₂ O-Ph | H | Me |
| 104 | NH ₂ | 4-CF ₃ O-Ph | H | Me |
| 105 | NH ₂ | F-4-MeO-Ph | H | Me |
| 106 | NH ₂ | 3-F-4-MeO-Ph | H | Me |
| 107 | NH ₂ | 3-F-4-MeO-Ph | Me | H |
| 108 | NH ₂ | 3-Me-4-MeO-Ph | H | H |
| 109 | NH ₂ | 3-Me-4-MeO-Ph | H | Me |

Table 2 (cont.)

| No. | R ¹ | R ² | R ³ | R ⁴ |
|-----|-----------------|-------------------|----------------|---------------------|
| 110 | NH ₂ | 3-Me-4-MeO-Ph | Me | H |
| 111 | NH ₂ | 3,4-diF-Ph | H | H |
| 112 | NH ₂ | 3,4-diF-Ph | H | Me |
| 113 | NH ₂ | 3,4-diF-Ph | Me | H |
| 114 | NH ₂ | 2,4-diF-Ph | H | H |
| 115 | NH ₂ | 2,4-diF-Ph | H | Me |
| 116 | NH ₂ | 2,4-diF-Ph | Me | H |
| 117 | NH ₂ | 3,4-diMe-Ph | H | H |
| 118 | NH ₂ | 3,4-diMe-Ph | H | Me |
| 119 | NH ₂ | 3,4-diMe-Ph | Me | H |
| 120 | NH ₂ | 2,4-diCl-Ph | H | H |
| 121 | NH ₂ | 2,4-diCl-Ph | H | Me |
| 122 | NH ₂ | 2,4-diCl-Ph | Me | H |
| 123 | NH ₂ | 3,4-diCl-Ph | H | H |
| 124 | NH ₂ | 3,4-diCl-Ph | H | Me |
| 125 | NH ₂ | 3,4-diCl-Ph | Me | H |
| 126 | NH ₂ | 3,4-di(MeO)-Ph | H | H |
| 127 | NH ₂ | 3,4-di(MeO)-Ph | H | Me |
| 128 | NH ₂ | 4-F-Ph | H | CH ₂ OH |
| 129 | NH ₂ | 4-F-Ph | H | CH ₂ OMe |
| 130 | NH ₂ | 4-MeO-Ph | H | CH ₂ OH |
| 131 | NH ₂ | 4-MeO-Ph | H | CH ₂ OMe |
| 132 | NH ₂ | 4-Cl-Ph | H | CH ₂ OH |
| 133 | NH ₂ | 4-Cl-Ph | H | CH ₂ OMe |
| 134 | NH ₂ | 4-Me-Ph | H | CH ₂ OH |
| 135 | NH ₂ | 4-Me-Ph | H | CH ₂ OMe |
| 136 | NH ₂ | 3,5-diCl-4-MeO-Ph | H | Me |
| 137 | NH ₂ | 3,5-diMe-4-MeO-Ph | H | Me |

The most preferable compounds represented by the formulae (I) and (II) are as follows:

- 3-methyl-2-(4-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole,
4-methyl-2-(4-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole,
5 1-(4-fluorophenyl)-2-(4-sulfamoylphenyl)pyrrole,
1-(4-fluorophenyl)-4-methyl-2-(4-sulfamoylphenyl)pyrrole,
5-fluoro-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole,
2-(4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole,
1-(4-methoxyphenyl)-4-methyl-2-(4-sulfamoylphenyl)pyrrole,
10 4-ethyl-2-(4-methoxyphenyl)-1-(4-sulfamoylphenyl)pyrrole,
2-(4-chlorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole,
4-methyl-2-(4-methylthiophenyl)-1-(4-sulfamoylphenyl)pyrrole,
2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole,
4-methyl-2-(4-methoxy-3-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole,
15 2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole,
4-methyl-2-phenyl-1-(4-sulfamoylphenyl)pyrrole,
4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl)pyrrole, and
2-(3-chloro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole.

Since the compound (I) of the present invention can form salts, "pharmaceutically acceptable salts thereof" means the salts. Such a salt can include alkali metal salts such as a sodium salt, a potassium salt and a lithium salt and alkaline earth metal salts such as a calcium salt and a magnesium salt.

The compounds of the invention may take up water upon exposure to the atmosphere to absorb water or to produce a hydrate. The present invention covers such hydrates.

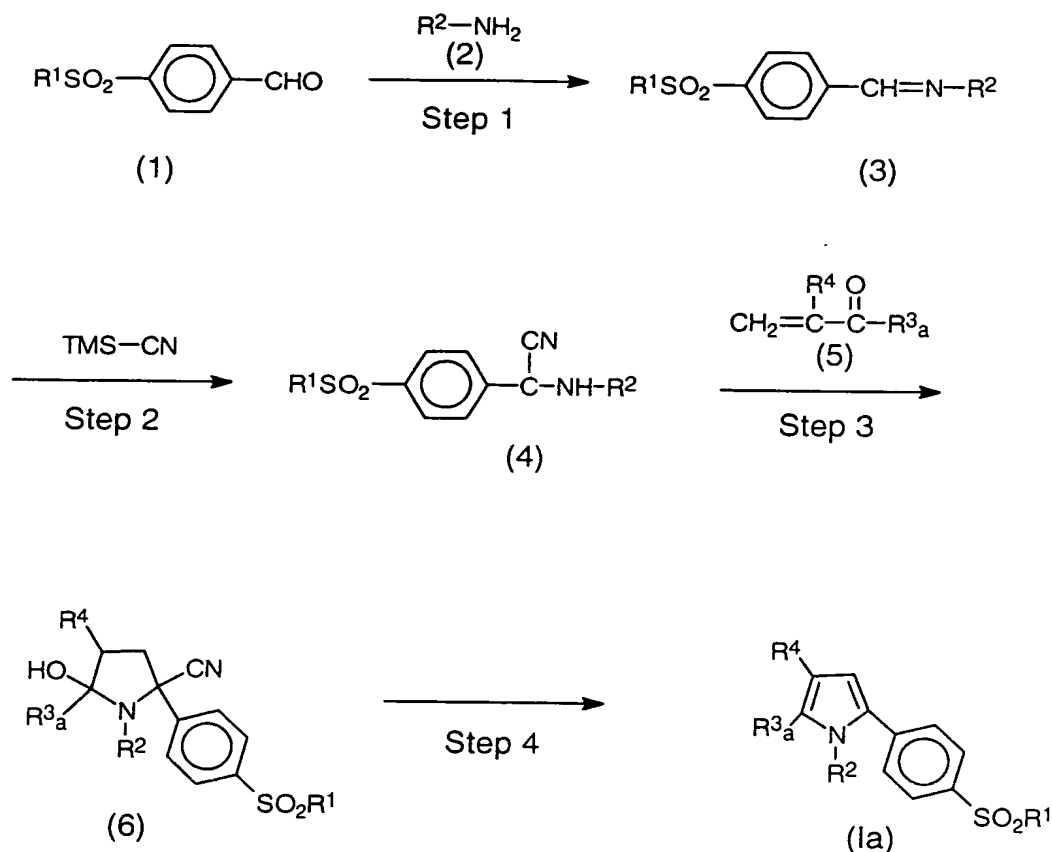
25 The compounds (I) of the present invention can have asymmetric carbon atoms in a molecule and each of isomer which is R and S isomers exists. Both isomers and a mixture thereof having an optional ratio are included in the present invention.

[Mode of the invention]

30 The compounds of the invention having formula (I) and (II) can be prepared by the following Methods A to H.

1. Preparation of the compounds having formula (I)

[Method A-1: A method for preparing the compound of formula (Ia) wherein R³ is a hydrogen atom, a lower alkyl group or a halogenated lower alkyl group]



(R¹, R² and R⁴ are as defined above, and R^{3a} represents a hydrogen atom, a lower alkyl group or a halogenated lower alkyl group.)

In Step 1, an aldimine compound of formula (3) is prepared by the dehydration condensation of a benzaldehyde compound of formula (1) with an aniline compound of formula (2) in an inert solvent.

There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane, heptane and petroleum ether; aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride and dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; alcohols, such as methanol, ethanol, propanol, isopropanol and butanol; and organic acids, such as acetic acid and propionic acid. Of these solvents, we prefer the alcohols.

Reaction temperature is normally from 5°C to 200°C (preferably from room temperature to 150°C). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature. However, reaction time is normally a period of from 10 minutes to 20 hours (preferably from 1 hour to 15 hours).

5 The reaction may be carried out while the water which is produced in the reaction is removed, but the reaction will normally proceed sufficiently without any such procedure.

In Step 2, an anilinonitrile compound of formula (4) is prepared by the addition of hydrogen cyanide to the aldimine compound of formula (3).

10 The reaction may be carried out by reacting the aldimine compound of formula (3) with trimethylsilyl cyanide in the presence of a Lewis acid (for example, aluminum chloride, tin chloride or zinc chloride) and an inert solvent (for example, aromatic hydrocarbons such as benzene, toluene and nitrobenzene; halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and 1,2-dichloroethane; and ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; of these, we prefer the ethers).

15 Reaction temperature is normally from 5°C to 200°C (preferably from room temperature to 150°C). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature. However, reaction time is normally a period of from 30 minutes to 100 hours (preferably from 1 hour to 30 hours).

20 In Step 3 and Step 4, the desired compound of formula (Ia), which is a compound of the present invention, is prepared by reacting the anilinonitrile compound of formula (4) with an α,β -unsaturated aldehyde or ketone compound of formula (5), to obtain a pyrrolidine compound of formula (6), which is then dehydrated and dehydrogencyanated in a modification of the method of V.A. Treibs, R. Derra [Ann. Chem. 589, 176 (1954)].

25 Step 3 is carried out in the presence of a base (for example, alkali metal hydroxides such as lithium hydroxide, sodium hydroxide and potassium hydroxide; alkali metal hydrides such as lithium hydride, sodium hydride and potassium hydride; alkali metal amides such as lithium amide, sodium amide, potassium amide and lithium bis(trimethylsilyl)amide; and alkali metal alkoxides such as lithium ethoxide, sodium methoxide, sodium ethoxide and
30 potassium t-butoxide, of these, we prefer the lithium amides) and in the presence of an inert solvent (for example, aliphatic hydrocarbons such as hexane and heptane; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as diethyl ether, diisopropyl

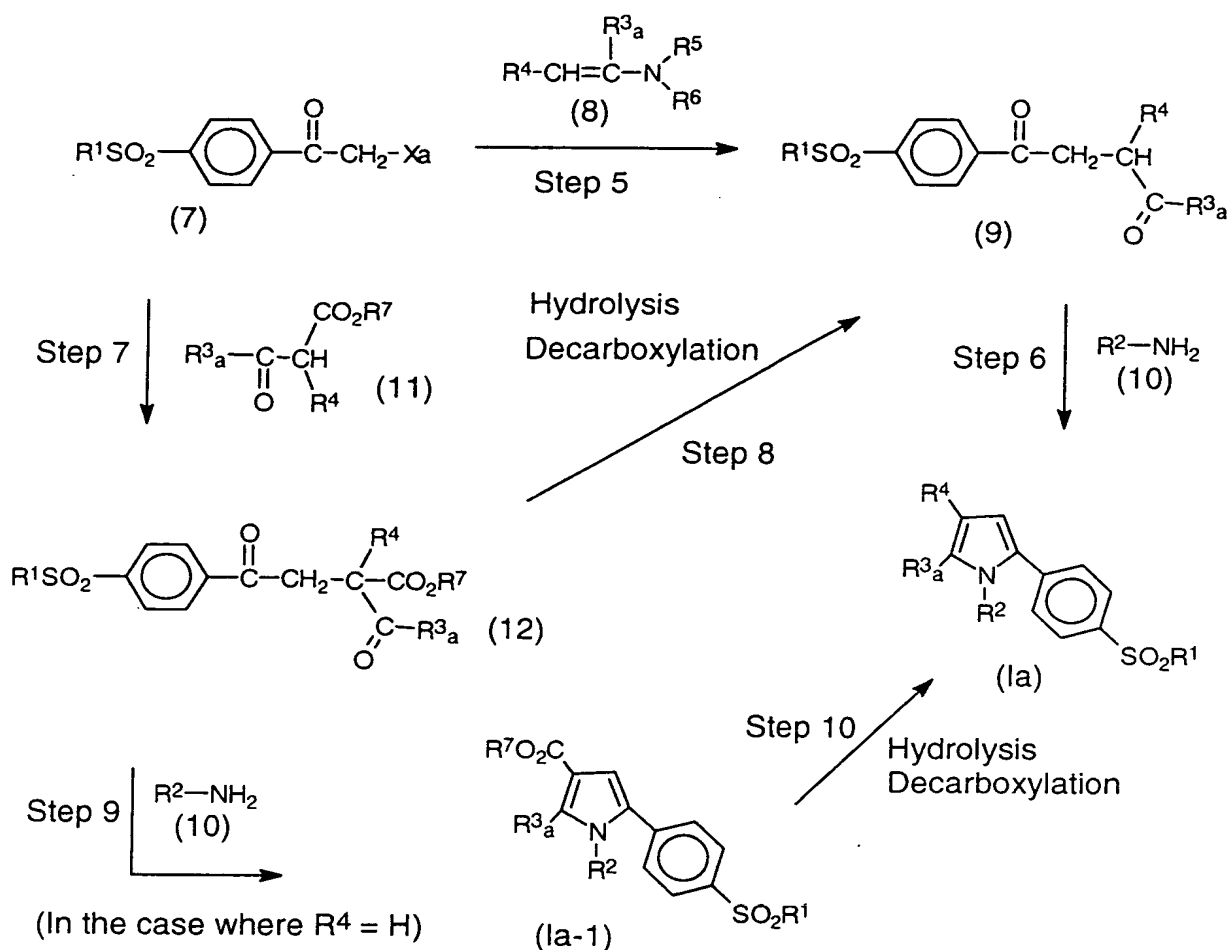
ether, tetrahydrofuran and dioxane; and alcohols such as methanol, ethanol, propanol, isopropanol and butanol, of these, we prefer the ethers).

5 The reaction temperatures is normally from -78°C to 100°C (preferably from -78°C to room temperature). The reaction time may vary widely, depending on many factors, notably the reaction temperature, but is normally a period of from 10 minutes to 30 hours (preferably from 1 hour to 20 hours).

10 In Step 4, the desired compound of formula (Ia), which is a compound of the present invention, is prepared by heating the residue obtained by distilling off the solvent, or by heating the material obtained by extracting that residue, washing it with water and distilling off the solvent, at a temperature not lower than 100°C, in the presence or absence of a solvent after completion of the reaction of Step 3. The reaction proceeds sufficiently in the absence of a solvent, but, when a solvent is used, the solvent is preferably inert and has a higher boiling point. Examples of suitable solvents include: toluene, xylene, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, diglyme and diphenyl ether.

15

[Method A-2: a modified method for preparing the compound of formula (Ia) wherein R³ represents a hydrogen atom, a lower alkyl group or a halogenated alkyl group]



(R^1 , R^2 , R^{3a} and R^4 are as defined above; each of R^5 and R^6 represents an alkyl group having from 1 to 4 carbon atoms or R^5 and R^6 together represent a heterocyclic ring containing 5 or 6 ring atoms, of which one may be a hetero atom selected from the group consisting of oxygen and sulfur atoms; R^7 represents a lower alkyl group; and X_a represents a chlorine, bromine or iodine atom.

In Step 5, a 1,4-dioxo compound of formula (9) is prepared by alkylating the β -position of the enamine compound of formula (8) with a phenacyl halide compound of formula (7).

The reaction is normally effected in the presence of an inert solvent (for example aliphatic hydrocarbons such as hexane, heptane and petroleum ether; aromatic hydrocarbons such as benzene, toluene and xylene; and ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane, of these, we prefer the ethers), in the presence or absence of a base (for example, pyridine, picoline, 4-(N,N-dimethylamino)pyridine, triethylamine, tributylamine, diisopropylethylamine and N-methylpiperidine).

The reaction temperature is normally from -30°C to 200°C (preferably from 0°C to 100°C). The reaction time may vary widely, depending on many factors, notably the reaction temperature, but, is normally a period of from 30 minutes to 30 hours (preferably from 1 hour to 20 hours).

5 At the end of this reaction, the reaction mixture is acidified, to prepare the 1,4-dioxo compound of formula (9).

10 In Step 6, the desired compound of formula (Ia) of the present invention is prepared by the dehydration condensation of the 1,4-dioxo compound of formula (9) and an aniline compound of formula (10) to close a ring. The reaction may be carried out under the same conditions as described in Step 1. However, it is preferred to carry out this step by heating under reflux in acetic acid for a period of from 1 hour to 10 hours.

 In Step 7, a dioxo ester compound of formula (12) is prepared by alkylating the α -position of the oxo ester compound of formula (11) with a phenacyl halide compound of formula (7).

15 The reaction is carried out in the presence of a base (for example, alkali metals such as lithium, sodium and potassium; alkali metal hydrides such as lithium hydride, sodium hydride and potassium hydride; alkali metal amides such as lithium amide, sodium amide and potassium amide; and alkali metal alkoxides such as lithium ethoxide, sodium methoxide, sodium ethoxide and potassium t-butoxide, of these, we prefer the alkali metal
20 alkoxides) and in the presence of an inert solvent (for example, aliphatic hydrocarbons such as hexane and heptane; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; amides such as dimethylformamide and dimethylacetamide; and alcohols such as methanol, ethanol, propanol, isopropanol, butanol and t-butanol, of these, we prefer the ethers or the alcohols).

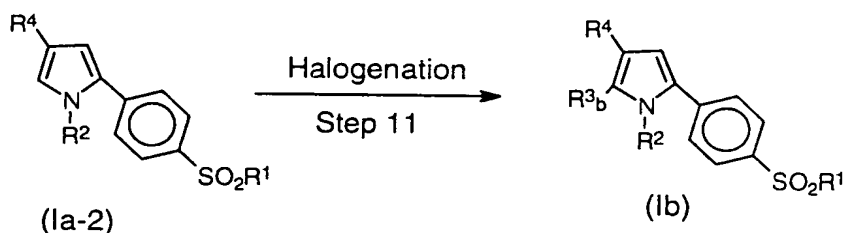
25 The reaction temperature is normally from 5°C to 200°C (preferably from room temperature to 150°C). The reaction time may vary widely, depending on many factors, notably the reaction temperature, but is normally a period of from 10 minutes to 20 hours (preferably from 30 minutes to 15 hours).

30 In Step 8, the 1,4-dioxo compound of formula (9) is prepared by carrying out decarboxylation of the dioxo ester compound of formula (12) at the same time as hydrolysis. The hydrolysis reaction may be carried out using any acid or alkali commonly used in organic synthesis chemistry for reactions of this type.

In Step 9 which may be conducted when R^4 in the dioxo ester compound of formula (12) is a hydrogen atom, the compound of formula (Ia-1) is prepared by reacting this compound with an aniline compound of formula (10). This reaction is essentially carried out in the same manner as described in Step 6.

5 In Step 10, the compound of formula (Ia) of the present invention is prepared by hydrolysing the ester portion of the compound of formula (Ia-1) to obtain the corresponding carboxylic acid, which is then decarboxylated. The hydrolysis reaction may be carried out by conventional methods as mentioned above. The decarboxylation reaction may be carried out using an acid or an alkali, or with heating, as is well known in the field of organic synthetic chemistry [for example, the method described in the Yakugaku Zasshi, 93(5), 584-598 (1973)].

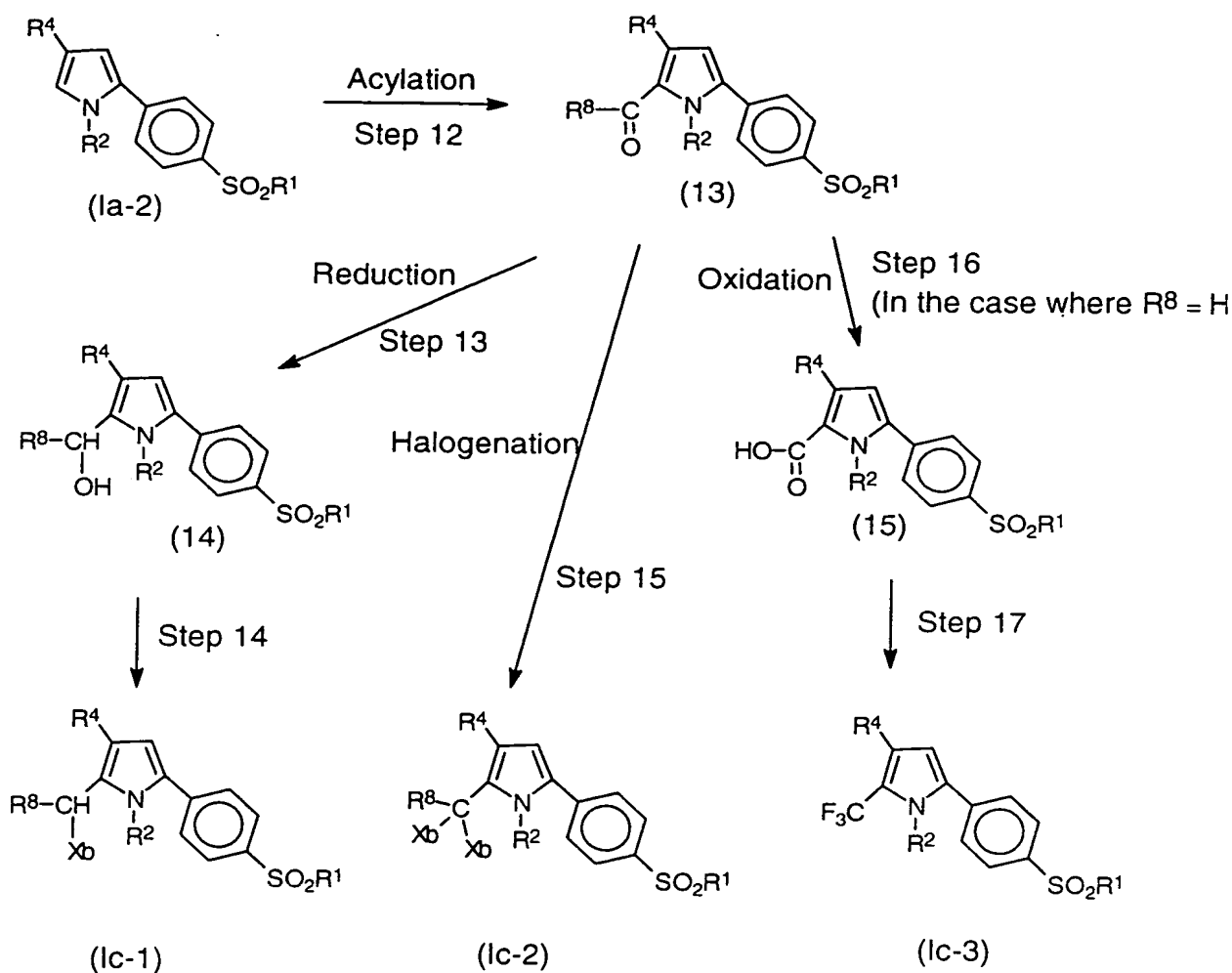
[Method B: a method of preparing a compound of formula (Ib) wherein R^3 is a halogen atom]



15 (R^1 , R^2 and R^4 are as defined above, and R^{3b} represents a halogen atom.)

In Step 11, the desired compound of formula (Ib) of the present invention is prepared by halogenating the compound of formula (Ia-2) of the present invention, which may have been prepared as described in either Method A-1 or Method A-2. Examples of suitable halogenation methods include: fluorination by, for example, xenon difluoride; chlorination by, for example, chlorine, sulfonyl chloride or N-chlorosuccinimide; bromination by, for example, bromine or N-bromosuccinimide; and iodination by, for example, iodine or N-iodosuccinimide. The reaction may be carried out according to the methods described in detail in "The Chemistry of Heterocyclic Compounds", Vol 48, Part 1, p348-395, published by John Wiley & Sons.

25 [Method C: a method of preparing a compound of formula (Ic-1), (Ic-2) or (Ic-3) wherein R^3 represents a halogenated lower alkyl group]



(R¹, R² and R⁴ are as defined above; R⁸ represents a hydrogen atom or a lower alkyl group; and X_b represents a halogen atom.)

- 5 In Step 12, an acylpyrrole compound of formula (13) is prepared by acylating a compound of formula (Ia-2) of the present invention. In this Step, a compound of formula (13) wherein R⁸ represents a hydrogen atom may be prepared by reacting a Vilsmeier reagent, such as phosphorus oxychloride-dimethylformamide, phosphorus oxybromide-dimethylformamide or oxalyl chloride-dimethylformamide, with the compound of formula
- 10 (Ia-2) in the presence of an inert solvent (for example, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and 1,2-dichloroethane; and amides such as dimethylformamide) at the temperature of from -10°C to 150°C (preferably from 0°C to 100°C) for a period of from 15 minutes to 20 hours (preferably from 30 minutes to 10 hours).

Those compounds of formula (13) wherein R^8 represents an alkyl group having from 1 to 3 carbon atoms may be prepared by reacting an acid anhydride or an acid halide of formula $(R^{8a}CO)_2O$ or $R^{8a}COX_a$ (wherein X_a is as defined above, and R^{8a} represents an alkyl group having from 1 to 3 carbon atoms) with the compound of formula (Ia-2) in the presence of a Lewis acid (for example, aluminum chloride, tin chloride or zinc chloride) and in the presence of an inert solvent (for example, aromatic hydrocarbons such as benzene, toluene and nitrobenzene; halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and 1,2-dichloroethane; and carbon disulfide) at the temperature of from -10°C to 150°C (preferably from 0°C to 100°C) for a period of from 10 minutes to 20 hours (preferably from 30 minutes to 10 hours).

In Step 13, a hydroxy compound of formula (14) is prepared by reducing the acyl group of the acylpyrrole compound of formula (13). The reaction may be effected using a reducing agent (for example, sodium borohydride, lithium borohydride, lithium aluminum hydride, diisobutylaluminum hydride or borane) or by using catalytic reduction with hydrogen and may be carried out according to the methods described in detail in "Jikken Kagaku Koza", Vol 20, p1-30, fourth edition, compiled by Japan Chemical Association, published by Maruzen.

In Step 14, the desired compound of formula (Ic-1), which is a compound of the present invention, is prepared by halogenating the hydroxy group of the hydroxy compound of formula (14). Suitable halogenating methods include: fluorination by, for example, diethylamino sulfur trifluoride (DAST); chlorination by, for example, thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride or triphenylphosphine/carbon tetrachloride; bromination by, for example, hydrobromic acid, thionyl bromide, phosphorus tribromide or triphenylphosphine/carbon tetrabromide; and iodination by, for example, hydroiodic acid or phosphorus triiodide, may be carried out according to the methods described in detail in "Jikken Kagaku Koza", Vol 19, p384-390, 438-446 and 465-470, fourth edition, compiled by Japan Chemical Association, published by Maruzen.

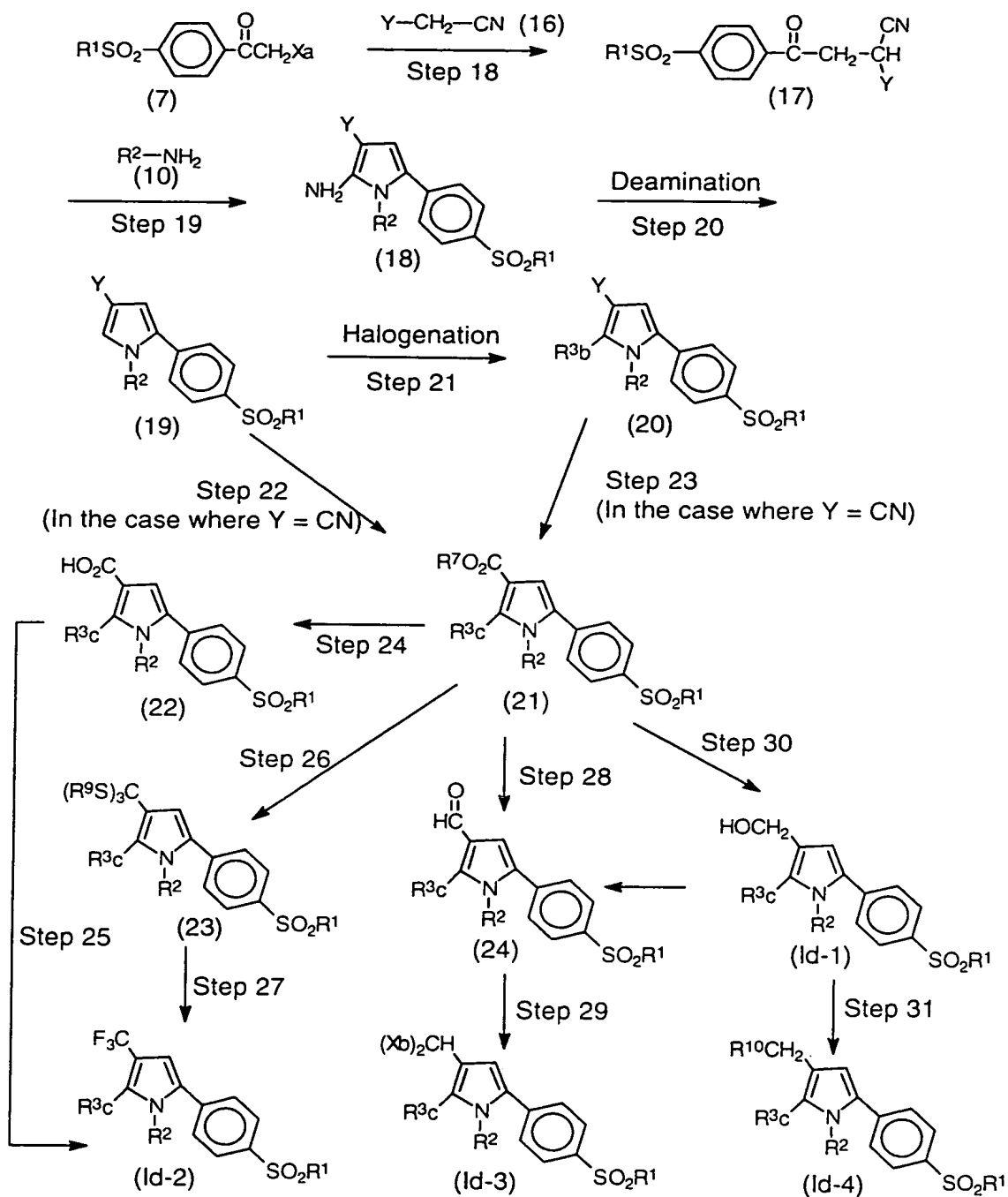
In Step 15, the desired compound of formula (Ic-2), which is a compound of the present invention, is prepared by gem-dihalogenating the carbonyl group of the acylpyrrole compound of formula (13), using a halogenating methods such as gem-difluorination by, for

example, sulfur tetrafluoride and DAST; gem-dichlorination by, for example, phosphorus pentachloride and thionyl chloride/dimethylformamide; gem-dibromination by, for example, boron tribromide; and gem-diiodination by, for example, trimethylsilyl iodide according to the methods described in detail in "Jikken Kagaku Koza", Vol 19, p390-392, 447-448 and 472, fourth edition, compiled by Japan Chemical Association, published by Maruzen.

In Step 16, a carboxylic acid compound of formula (15) is prepared by oxidizing an acylpyrrole compound of formula (13) wherein R^8 is a hydrogen atom, using, for example, potassium permanganate, chromic acid, hydrogen peroxide, nitric acid, and silver (I or II) oxide, according to the method described in detail in "Shin-Jikken Kagaku Koza" Vol 15, "Sanka to Kangen (Oxidation and Reduction)" [1-1], [1-2], compiled by Japan Chemical Association, published by Maruzen.

In Step 17, the desired compound of formula (Ic-3), which is a compound of the present invention, is prepared by converting the carboxy group of the carboxylic acid compound of formula (15) into a trifluoromethyl group. This Step may be carried out, for example, using sulfur tetrafluoride, according to the methods described in "Jikken Kagaku Koza", Vol 19, p390-392, fourth edition, compiled by Japan Chemical Association, published by Maruzen.

[Method D: a method of preparing compounds of formula (Id-1), (Id-2), (Id-3) or (Id-4) wherein R^4 represents a substituted alkyl group and R^3 represents a hydrogen atom or a halogen atom]



$(\text{R}^1, \text{R}^2, \text{R}^{3b}, \text{R}^7, \text{X}_a \text{ and } \text{X}_b \text{ are as defined above; } \text{R}^{3c} \text{ represents a hydrogen atom or a halogen atom; } \text{R}^9 \text{ represents a lower alkyl group; } \text{R}^{10} \text{ represents a halogen atom or a lower alkoxy group; and; Y represents a cyano group or a group of formula } -\text{CO}_2\text{R}^7 \text{ (where } \text{R}^7 \text{ is as defined above).}$

In Step 18, a phenacyl acetonitrile compound of formula (17) is prepared by alkylating the cyano compound of formula (16) with a phenacyl halide compound of formula (7), in the same manner as described in Step 7.

5 In Step 19, an aminopyrrole compound of formula (18) is prepared by reacting the phenacylacetonitrile compound of formula (17) with an aniline compound of formula (10). This step may be carried out in the presence of a catalytic amount of hydrogen chloride according to the methods described by K.M.H. Hilmy & E.B. Pedersen [Liebigs Ann. Chem. (1989), 1145-1146].

10 In Step 20, a pyrrole compound of formula (19) is prepared by removing an amino group from the aminopyrrole compound of formula (18), by reacting an alkyl nitrite (for example, methyl nitrite, ethyl nitrite, propyl nitrite, butyl nitrite, t-butyl nitrite or isoamyl nitrite) with the aminopyrrole compound of formula (18), in the presence of an inert solvent (for example, aliphatic hydrocarbons such as hexane or heptane; aromatic hydrocarbons such as benzene, toluene or xylene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran or dioxane; and amides such as dimethylformamide or dimethylacetamide, of these, we prefer
15 the ethers) at the temperature of from -10°C to 200°C (preferably from room temperature to 150°C) for a period of from 10 minutes to 20 hours (preferably from 30 minutes to 15 hours).

In Step 21, a halopyrrole compound of formula (20) is prepared by halogenating the pyrrole compound of formula (19) in the same manner as described in Step 11.

20 In Step 22 and Step 23, an ester compound of formula (21) is prepared from a compound of formula (19) or (20) in which Y represents a cyano group, by converting the cyano group into an alkoxycarbonyl group. The steps may be carried out by using, for example, the compound of formula (19) or (20), appropriate alcohols and acids such as hydrochloric acid, sulfuric acid or p-toluenesulfonic acid, using the methods described in
25 "Shin-Jikken Kagaku Koza" Vol 14, p1022-1023, compiled by Japan Chemical Association, published by Maruzen.

In Step 24, a carboxylic acid compound of formula (22) is prepared by hydrolysing the ester compound of formula (21). This reaction may be carried out in the same manner as the hydrolysis reaction described in Step 8.

In Step 25, the desired compound of formula (Id-2) of the present invention is prepared by converting the carboxy group of the carboxylic acid compound of formula (22) into a trifluoromethyl group. This reaction may be carried out in the same manner as described in Step 17.

5 Step 26 and Step 27 together provide an alternative method of preparing the compound of formula (Id-2) of the present invention from the ester compound of formula (21). In Step 26, first, the alkoxycarbonyl group of the ester compound of formula (21) is converted into a tri(alkylthio)methyl group, which is then converted into a trifluoromethyl group by an oxidative fluorodesulfurization reaction. This method is described in detail by D.P.
10 Matthews, J.P. Whitten & J.R. McCarthy [Tetrahedron Letters, 27(40), 4861-4864, (1986)].

 In Step 28, the corresponding aldehyde compound of formula (24) is prepared by reducing the alkoxycarbonyl group of the ester compound of formula (21). For example, this step may be carried out by using lithium aluminum hydride, sodium aluminum hydride, lithium triethoxyaluminum hydride, diisobutylaluminum hydride, etc. according to the
15 methods described in detail in "Shin-Jikken Kagaku Koza" Vol 14, p656-659, compiled by Japan Chemical Association, published by Maruzen.

 In Step 29, the desired compound of formula (Id-3) of the present invention is prepared by gem-dihalogenating the aldehyde compound of formula (24). This reaction may be carried out in the same manner as described in Step 15.

20 In Step 30, a hydroxymethyl compound of formula (Id-1), a desired compound of the present invention, is prepared by reducing the alkoxycarbonyl group of the ester compound of formula (21). For example, this step may be carried out using lithium aluminum hydride, lithium borohydride, isobutylaluminum hydride, etc. according to the methods described in detail in "Jikken Kagaku Koza" Vol 20, p12-14, fourth edition, compiled by Japan Chemical
25 Association, published by Maruzen.

 In Step 31, the halomethyl compound or the alkoxymethyl compound of formula (Id-4), which are compounds of the present invention, are prepared by halogenating or etherifying a hydroxymethyl compound of formula (Id-1). In this step, the halogenation reaction may be carried out in the same manner as described in Step 14.

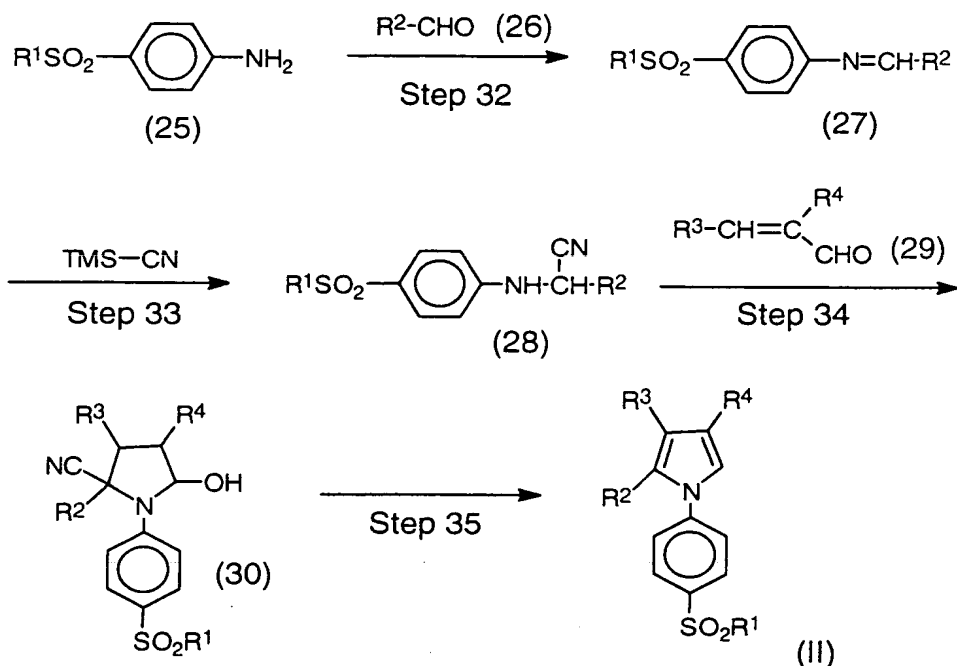
30 The etherification reaction may be carried out by reacting the hydroxymethyl compound of formula (Id-1) with an alkyl halide in the presence of an inert solvent (for

example, aliphatic hydrocarbons such as hexane, heptane and petroleum ether; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; and amides such as dimethylformamide and dimethylacetamide, of these, we prefer the ethers and the amides) and in the presence of a

base (for example, alkali metal hydrides such as lithium hydride, sodium hydride and potassium hydride; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t-butoxide; and tertiary amines such as triethylamine, tributylamine, pyridine, picoline and 4-(N,N-dimethylamino)pyridine, of these, we prefer sodium hydride or potassium t-butoxide) at the temperature of from -10°C to 200°C (preferably from 0°C to 150°C) for a period of from 30 minutes to 48 hours (preferably from 1 hour to 24 hours).

2. A method of preparing compounds of formula (II)

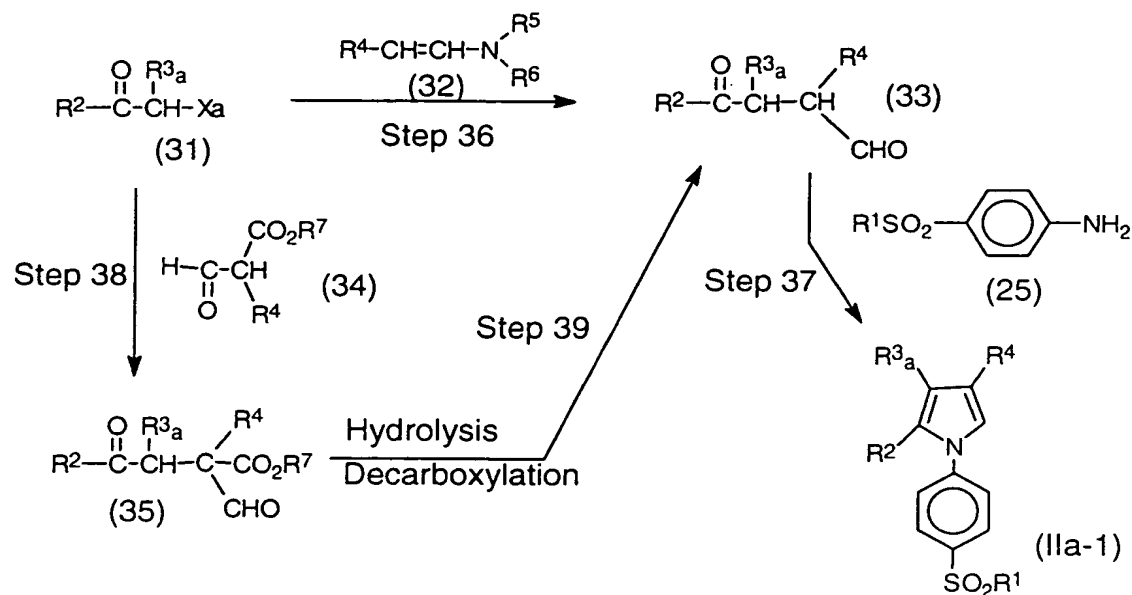
[Method E: a method of preparing compounds of formula (II)]



(R^1 , R^2 , R^3 and R^4 are as defined above.)

The compound of formula (II), a desired compound of the present invention, is prepared by reacting the aniline compound of formula (25) and benzaldehyde compound of formula (26) according to the reactions of Step 32, Step 33, Step 34 and Step 35. Each reaction in these Steps may be carried out in the same manner as described in Step 1, Step 2, Step 3 and Step 4, respectively.

[Method F: a method of preparing compounds of formula (IIa-1) wherein R³ represents a hydrogen atom, a lower alkyl group or a halogenated lower alkyl group]



(R¹, R², R^{3a}, R⁴, R⁵, R⁶, R⁷ and X_a are as defined above.)

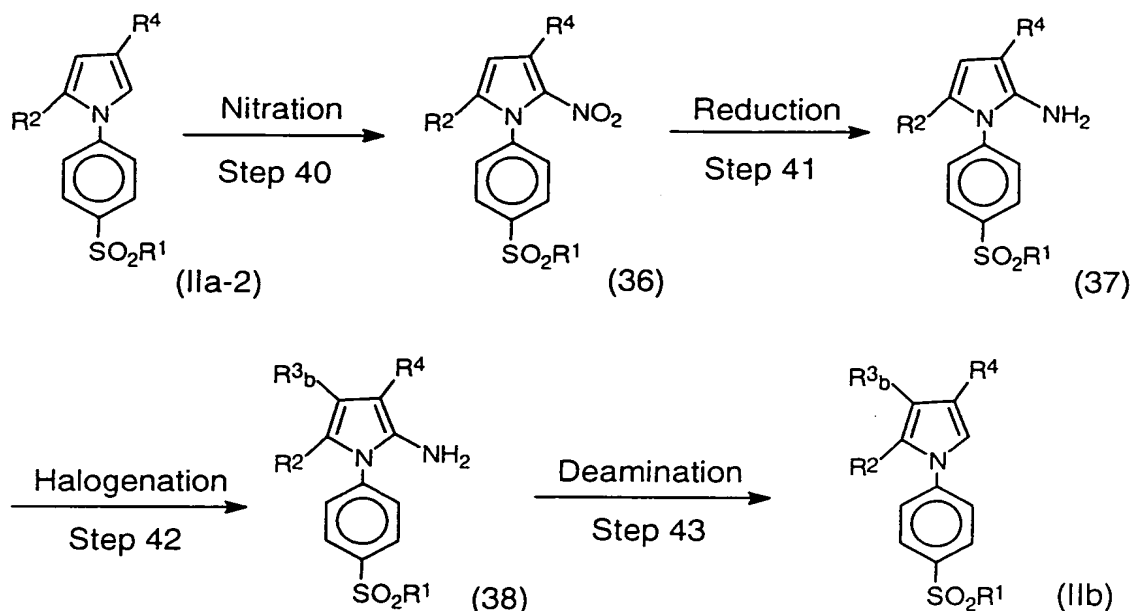
5 In Step 36, a 1,4-dioxo compound of formula (33) is prepared by alkylating the β-position of an enamine compound of formula (32) using a phenacyl halide compound of formula (31) in the same manner as described in Step 5.

In Step 37, the compound of formula (IIa-1), which is a compound of the present invention, is prepared by the dehydration-condensation of the 1,4-dioxo compound of
10 formula (33) and the aniline compound of formula (25) to close a ring in the same manner as described in Step 6.

In Step 38, a dioxo ester compound of formula (35) is prepared by alkylating the α-position of a formyl ester compound of formula (34) with the phenacyl halide compound of formula (31) in the same manner as described in Step 7.

15 In Step 39, the 1,4-dioxo compound of formula (33) is prepared by carrying out decarboxylation of the dioxo ester compound of formula (35) at the same time as hydrolysis, in the same manner as described in Step 8.

[Method G: a method of preparing compounds of formula (IIb) wherein R³ represents a halogen atom]



(R^1 , R^2 , R^{3b} and R^4 are as defined above.)

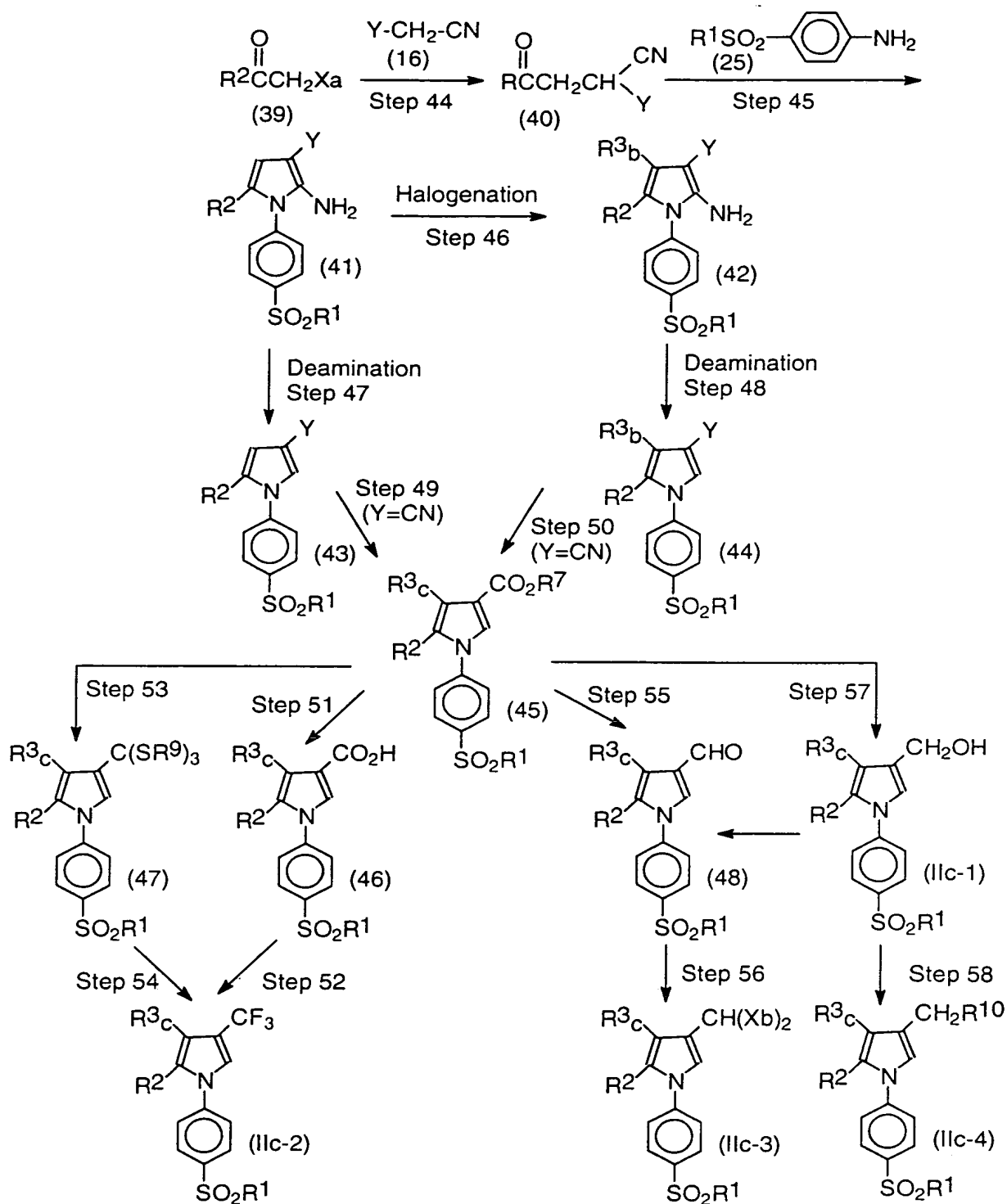
In Step 40, a nitropyrrole compound of formula (36) is prepared by nitrating the compound of formula (IIa-2). This step is carried out by using, for example, nitric acid, fuming nitric acid, or nitric acid/acetic anhydride, according to the methods described in detail in "The Chemistry of Heterocyclic Compounds", Vol 48, Part 1, p330-345, published by John Wiley & Sons.

In Step 41, an aminopyrrole compound of formula (37) is prepared by reducing a nitro group of the nitropyrrole compound of formula (36). Methods of reducing nitro groups are well known in the field of organic synthetic chemistry, and any conventional method may be used.

In Step 42, an aminohalopyrrole compound of formula (38) is prepared by halogenating the aminopyrrole compound of formula (37) in the same manner as described in Step 11.

In Step 43, the desired compound of formula (IIb) of the present invention is prepared by removing the amino group from the aminohalopyrrole compound of formula (38) in the same manner as described in Step 20.

[Method H: a method of preparing compounds of formula (IIc-1), (IIc-2), (IIc-3) or (IIc-4) wherein R^4 represents a substituted alkyl group and R^3 represents a hydrogen atom or a halogen atom]



(R¹, R², R^{3b}, R^{3c}, R⁷, R⁹, R¹⁰, X_a, X_b and Y are as defined above.)

The present method is composed of Step 44 to Step 58.

In Step 44, a compound of formula (40) is prepared by alkylating the cyano compound of formula (16) with a phenacyl halide compound of formula (39). This reaction is essentially the same as described in Step 18 mentioned above.

In Step 45, an aminopyrrole compound of formula (41) is prepared by reacting the phenacylacetonitrile compound of formula (40) with the aniline compound of formula (25). This reaction is essentially the same as described in Step 19 mentioned above.

In Step 46, an aminohalogeno compound of formula (42) is prepared by halogenating the aminopyrrole compound of formula (41). This reaction is essentially the same as described in Step 42 mentioned above.

In Step 47 and Step 48, a compound of formula (43) and a compound of formula (44) are prepared by removing the amino group from the aminopyrrole compound of formula (41) and the aminohalogeno compound of formula (42), respectively. This reaction is essentially the same as described in Step 43 mentioned above.

In Step 49 and Step 50, an ester compound of formula (45) is prepared from those pyrrole compounds of formulae (43) and (44) in which Y represents a cyano group by converting the cyano group to an alkoxycarbonyl group. This reaction is essentially the same as described in Step 22 and Step 23 mentioned above.

In Step 51 and Step 52, a trifluoromethyl compound of formula (IIc-2), a desired compound of the present invention, is prepared from the ester compound of formula (45), via a carboxylic acid compound of formula (46). This reaction is essentially the same as described in Step 24 and Step 25 mentioned above, respectively.

These Step 53 and Step 54 provide an alternative route for preparing the trifluoromethyl compound of formula (IIc-2) from the ester compound of formula (45), via a tri(alkylthio)methyl compound of formula (47). This reaction is essentially the same as described in Step 26 and Step 27 mentioned above, respectively.

In Step 55 and Step 56, a dihalomethyl compound of formula (IIc-3), a desired compound of the present invention, is prepared from the ester compound of formula (45), via an aldehyde compound of formula (48). This reaction is essentially the same as described in Step 28 and Step 29 mentioned above, respectively.

In Step 57 and Step 58, the desired compound of formula (IIc-4), which is a compound of the present invention, is prepared from the ester compound of formula (45), via a hydroxymethyl compound of formula (IIc-1), which is also a compound of the present

invention. This reaction is essentially the same as described in Step 30 and Step 31 mentioned above, respectively.

The aldehyde compound of formula (24) in Method D and the aldehyde compound of formula (48) in Method H can be also prepared from the corresponding hydroxymethyl compounds of formulae (Id-1) and (IIc-1), respectively. The reaction in which a hydroxymethyl group is converted to a formyl group may be carried out using, for example, chromic acid, manganese dioxide or dimethyl sulfoxide, according to the methods described in detail in "Jikken Kagaku Koza" Vol 21, p1-23, fourth edition, compiled by Japan Chemical Association, published by Maruzen.

In the formula (I) or (II), in the case where a compound wherein R^1 is methyl group is prepared, the corresponding methylthio compound ($-SCH_3$) is used instead of methylsulfonyl compound ($-SO_2CH_3$), as the starting material or the side material, and the reaction is carried out in the same manner as described in all reaction steps mentioned above, to obtain the corresponding methylthio compound as an intermediate, respectively and the desired methylsulfonyl compounds can be obtained by oxidizing these methylthio compounds. It is possible to convert the methylthio group into the methylsulfonyl group in any steps and to obtain the desired compound of the formula (I) or (II) wherein R^1 is methyl group by reacting the methylsulfonyl compound thus obtained in the same manner as described above,

The oxidation reaction of from a methylthio compound to a methylsulfonyl compound is carried out by reacting an oxidizing agent (for example, peracids such as peracetic acid, perbenzoic acid and m-chloroperbenzoic acid; hydrogen peroxide; alkali metal perhalogenate such as sodium metaperchlorate, sodium metaperiodate and potassium metaperiodate, preferably peracids or hydrogen peroxide, particularly preferably m-chloroperbenzoic acid) with a methylthio compound in an inert solvent (for example, aliphatic hydrocarbons such as hexane, heptane and petroleum ether; aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and dichloroethane; alcohols such as methanol, ethanol, propanol and butanol; esters such as ethyl acetate, propyl acetate, butyl acetate and ethyl propionate; carboxylic acids such as acetic acid and propionic acid; water; or a mixture of any two or more of these solvent, preferably halogenated hydrocarbons (particularly, methylene chloride, chloroform, or dichloroethane) or carboxylic acids, (particularly, acetic acid) at -20°C to 150°C

(preferably, 0°C to 100°C) for a period of 10 minutes to 10 hours (preferably, 30 minutes to 5 hours).

The 1,2-diphenylpyrrole derivatives of the present invention and pharmaceutically acceptable salts thereof act as cyclooxygenase-2 selective inhibiting agents and/or as inflammatory cytokine production suppressing agents, and are thus effective for the prophylaxis and therapy of diseases mediated by cyclooxygenase-2 and/or inflammatory cytokines and can be served as an analgesic, anti-inflammatory agent and/or antipyretic. These types of analgesics, anti-inflammatory agents and/or antipyretics exhibit effects not only on inflammatory diseases, such as pain, pyrexia, and edema, but also on chronic inflammatory diseases, such as chronic rheumatoid arthritis and osteoarthritis, allergic inflammatory diseases, asthma, sepsis, psoriasis, various autoimmune diseases, systemic lupus erythematosus, juvenile onset diabetes, autoimmune intestinal diseases (such as ulcerative colitis, Crohn's disease), viral infection, tumors and glomerulonephritis.

The 1,2-diphenylpyrrole derivatives of the present invention can be administered by orally, for example, in the form of tablets, capsules, granules, powders or syrups; or by parenterally, for example, in the form of injection, suppositories or ointments. These pharmaceutical formulations can be prepared by mixing the compounds of the present invention with the additives used usually, such as excipients, binders, disintegrating agents, lubricants, stabilizers, corrigents in well known methods. The dose varies depending on the condition, age and weight of the patient, administration route, the type of the disease, etc., but the compounds of the present invention can be usually administered in a daily dose of 0.1 to 50 mg/kg body weight in the case of adult, either in a single dose or divided doses.

[EXAMPLES]

[EXAMPLE 1]

1-(4-Methoxyphenyl)-2-(4-methylsulfonylphenyl)pyrrole

1) 4-Methoxy-N-(4-methylsulfonylbenzylidene)aniline

1.00 g (5.4 mmol) of 4-methylsulfonylbenzaldehyde and 0.67 g (5.4 mmol) of 4-methoxyaniline were dissolved in 15 ml of ethanol, and the solution was heated under reflux for 1 hour. At the end of this time, the reaction solution was cooled to room temperature, and the crystals which precipitated were collected by filtration and washed with ethanol, to give

1.48 g (yield 95 %) of 4-methoxy-N-(4-methylsulfonylbenzylidene)aniline as slightly yellow prismatic crystals.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

8.57 (1H, singlet); 8.11 - 8.01 (4H, multiplet); 7.33 - 7.26 (2H, multiplet); 6.99 - 6.93 (2H, multiplet); 3.85 (3H, singlet); 3.09 (3H, singlet).

2) α -(4-Methoxyanilino)-4-methylsulfonylphenylacetonitrile

1.48 g (5.1 mmol) of 4-methoxy-N-(4-methylsulfonylbenzylidene)aniline [prepared as described in step 1)] were suspended in 15 ml of anhydrous tetrahydrofuran, and 0.80 ml (6.0 mmol) of 95% trimethylsilyl cyanide and 0.85 g (6.0 mmol) of zinc chloride were added to the resulting suspension at 0°C, whilst stirring. The temperature of the reaction mixture was then allowed to return to room temperature, and the mixture was stirred overnight. At the end of this time, water was added and the mixture was extracted with ethyl acetate. The organic extract was washed with water and dried over anhydrous sodium sulfate, after which it was concentrated by evaporation under reduced pressure and the crystals which precipitated were collected by filtration, to give 1.05 g (yield 65%) of the title compound as a slightly yellow powder.

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.04 (1H, doublet, $J = 8$ Hz); 7.84 (2H, doublet, $J = 8$ Hz); 6.84 (4H, singlet); 6.45 (1H, doublet, $J = 10$ Hz); 6.10 (1H, doublet, $J = 10$ Hz); 3.67 (3H, singlet); 3.25 (3H, singlet).

3) 1-(4-Methoxyphenyl)-2-(4-methylsulfonylphenyl)pyrrole

1.00 g (3.2 mmol) of α -(4-methoxyanilino)-4-methylsulfonylphenylacetonitrile [prepared as described in step 2)] was suspended in 15 ml of anhydrous tetrahydrofuran, and 0.24 ml (3.5 mmol) of acrolein was added to the resulting suspension. 3.2 ml (3.2 mmol) of a 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran were then added dropwise to the mixture at -60°C to -65°C, whilst stirring. The mixture was stirred at the same temperature for 1 hour, and then the temperature of the mixture was allowed to return to room temperature, and the mixture was stirred for a further 1.5 hours. At the end of this time, a saturated aqueous solution of ammonium chloride was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic extract was washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure, and the residue was heated at 200°C for 1 hour. It was then applied to a

silica gel chromatography column, and eluted with a 1 : 9 by volume mixture of hexane and methylene chloride, to give 0.32 g (yield 31%) of the title compound as a pale yellow powder, melting at 148 - 149°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

- 5 7.74 (2H, doublet, J = 8 Hz); 7.27 (2H, doublet, J = 8 Hz); 7.13 - 7.07 (2H, multiplet); 6.95 - 6.85 (3H, multiplet); 6.58 - 6.57 (1H, multiplet); 6.39 - 6.36 (1H, multiplet); 3.84 (3H, singlet); 3.04 (3H, singlet).

[EXAMPLE 2]

10 1-(4-Chlorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 4-chloroaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a pale yellow powder, melting at 184 - 188°C. The yield of the compound (pale yellow prismatic crystals) in the first stage was 94%, that in the second stage
15 (white powder) was 93%, and that in the third stage was 42%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.78 (2H, doublet, J = 8 Hz); 7.37 - 7.26 (4H, multiplet); 7.13 - 7.09 (2H, multiplet); 6.97 (1H, singlet); 6.58 - 6.57 (1H, multiplet); 6.42 - 6.39 (1H, multiplet); 3.05 (3H, singlet).

20 [EXAMPLE 3]

1-(4-Trifluoromethylphenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 4-trifluoromethylaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a white powder, melting at 187 - 190°C. The yield of the
25 compound (pale yellow prismatic crystals) in the first stage was 64%, that in the second stage (white powder) was 95%, and that in the third stage was 47%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.80 (2H, doublet, J = 8 Hz); 7.64 (2H, doublet, J = 8 Hz); 7.28 (4H, doublet, J = 10 Hz); 7.02 (1H, singlet); 6.61 - 6.60 (1H, multiplet); 6.46 - 6.43 (1H, multiplet); 3.06 (3H, singlet).

30

[EXAMPLE 4]

1-(4-Trifluoromethoxyphenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 4-trifluoromethoxyaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a white powder, melting at 150 - 152°C. The yield of the compound (pale yellow prismatic crystals) in the first stage was 59%, that in the second stage (white powder) was 97%, and that in the third stage was 52%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.78 (2H, doublet, J = 8 Hz); 7.29 - 7.18 (6H, multiplet); 6.98 (1H, singlet); 6.59 - 6.58 (1H, multiplet); 6.43 - 6.41 (1H, multiplet); 3.05 (3H, singlet).

10 [EXAMPLE 5]

1-(3-Chloro-4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 3-chloro-4-fluoroaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a pale yellow powder, melting at 146 - 149°C. The yield of the compound (white powder) in the first stage was 93%, that in the second stage (white powder) was 96%, and that in the third stage was 39%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.80 (2H, doublet, J = 8 Hz); 7.33 - 6.95 (6H, multiplet); 6.57 (1H, doublet, J = 2 Hz); 6.41 - 6.39 (1H, multiplet); 3.05 (3H, singlet).

20

[EXAMPLE 6]

1-(3,4-Difluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 3,4-difluoroaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a pale yellow powder, melting at 137 - 139°C. The yield of the compound (pale yellow prismatic crystals) in the first stage was 66%, that in the second stage (white powder) was 92%, and that in the third stage was 46%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.80 (2H, doublet, J = 8 Hz); 7.28 (2H, doublet, J = 8 Hz); 7.22 - 6.87 (6H, multiplet); 6.58 - 6.56 (1H, multiplet); 6.42 - 6.39 (1H, multiplet); 3.06 (3H, singlet).

30

[EXAMPLE 7]

1-(2,4-Difluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 2,4-difluoroaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a white powder, melting at 122 - 125°C. The yield of the compound (white powder) in the first stage was 79%, that in the second stage (white powder) was 97%, and that in the third stage was 10%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.77 (2H, doublet, J = 8 Hz); 7.30 - 7.19 (3H, multiplet); 6.95 - 6.89 (3H, multiplet); 6.60 - 6.59 (1H, multiplet); 6.45 - 6.42 (1H, multiplet); 3.04 (3H, singlet).

[EXAMPLE 8]

1-(3,4-Dimethylphenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 3,4-dimethylaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a white powder, melting at 134 - 137°C. The yield of the compound (yellow prismatic crystals) in the first stage was 95%, that in the second stage (white powder) was 96%, and that in the third stage was 23%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.74 (2H, doublet, J = 8 Hz); 7.29 (2H, doublet, J = 8 Hz); 7.10 - 6.82 (4H, multiplet); 6.57 - 6.55 (1H, multiplet); 6.38 - 6.36 (1H, multiplet); 3.03 (3H, singlet); 2.29 (3H, singlet); 2.24 (3H, singlet).

[EXAMPLE 9]

1-(4-Methylphenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 4-methylaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a pale yellow powder, melting at 112 - 114°C. The yield of the compound (white powder) in the first stage was 97%, that in the second stage (white powder) was 98%, and that in the third stage was 19%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.74 (2H, doublet, J = 8 Hz); 7.28 (2H, doublet, J = 9 Hz); 7.16 (2H, doublet, J = 8 Hz); 7.05 (2H, doublet, J = 8 Hz); 6.97 (1H, multiplet); 6.57 - 6.56 (1H, multiplet); 6.39 - 6.37 (1H, multiplet); 3.03 (3H, singlet); 2.39 (3H, singlet).

5 [EXAMPLE 10]

1-(3,4-Dichlorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 3,4-dichloroaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a white powder, melting at 139 - 142°C. The yield of the
10 compound (white powder) in the first stage was 91%, that in the second stage (white powder) was 93%, and that in the third stage was 41%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.83 (2H, doublet, J = 8 Hz); 7.43 - 7.26 (4H, multiplet); 6.96 - 6.91 (4H, multiplet); 6.58 - 6.57 (1H, multiplet); 6.43 - 6.41 (1H, multiplet); 3.06 (3H, singlet).

15

[EXAMPLE 11]

1-(3,4-Methylenedioxyphenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 3,4-methylenedioxyaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a pale yellow powder, melting at 172 -
20 175°C. The yield of the compound (pale yellow powder) in the first stage was 95%, that in the second stage (grey powder) was 91%, and that in the third stage was 29%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.77 (2H, doublet, J = 9 Hz); 7.31 (2H, doublet, J = 9 Hz); 6.93 (1H, singlet); 6.78 (1H, doublet, J = 8 Hz); 6.66 (2H, doublet, J = 8 Hz); 6.55 (1H, singlet); 6.37 - 6.35 (1H, multiplet); 6.03 (2H, singlet); 3.05 (3H, singlet).

25

[EXAMPLE 12]

1-(4-Methoxyphenyl)-4-methyl-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using methacrolein instead of acrolein, the title compound was obtained as a pale yellow powder (yield 21%), melting at 154 - 160°C.

30

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.72 (2H, doublet, J = 8 Hz); 7.25 (2H, doublet, J = 8 Hz); 7.09 - 7.03 (2H, multiplet); 6.89 - 6.84 (2H, multiplet); 6.73 (1H, singlet); 6.41 (1H, doublet, J = 2 Hz); 3.83 (3H, singlet); 3.03 (3H, singlet); 2.18 (3H, singlet).

5

[EXAMPLE 13]

2-(4-Fluorophenyl)-1-(4-sulfamoylphenyl)pyrrole

1) N-(4-Fluorobenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 4-fluorobenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a white powder (yield 63%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated acetone) δ ppm:

8.64 (1H, singlet); 8.12 - 8.03 (2H, multiplet); 7.93 (2H, doublet, J = 9 Hz); 7.40 - 7.28 (4H, multiplet); 6.57 (2H, singlet).

2) 4-Fluoro- α -(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-fluorobenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a white powder (yield 95%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.75 (2H, doublet, J = 9 Hz); 7.66 - 7.55 (2H, multiplet); 7.20 - 7.10 (2H, multiplet); 6.81 (2H, doublet, J = 9 Hz); 6.71 (1H, doublet, J = 8 Hz); 6.35 (2H, singlet); 5.61 (1H, doublet, J = 8 Hz).

3) 2-(4-Fluorophenyl)-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 4-fluoro- α -(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and acrolein as starting materials, the title compound was obtained as a brown powder (yield 11%), melting at 198 - 199°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.88 (2H, doublet, J = 9 Hz); 7.26 (2H, doublet, J = 9 Hz); 7.14 - 7.04 (2H, multiplet); 7.00 - 6.90 (3H, multiplet); 6.95 - 6.87 (2H, multiplet); 4.87 (2H, singlet).

Mass spectrum (EI) m/z: 316 [M⁺].

[EXAMPLE 14]

2-(4-Fluorophenyl)-3-methyl-1-(4-sulfamoylphenyl)pyrrole

5 Following a procedure similar to that described in Example 13-3), but using crotonaldehyde instead of acrolein, the title compound was obtained as a white powder (yield 19%), melting at 187 - 188°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.81 (2H, doublet, J = 9 Hz); 7.15 (2H, doublet, J = 9 Hz); 7.10 - 6.95 (2H, multiplet); 6.90
10 (2H, doublet, J = 3 Hz); 6.29 (2H, doublet, J = 3 Hz); 4.78 (2H, singlet); 2.14 (3H, singlet).

Mass spectrum (EI) m/z: 330 [M⁺].

[EXAMPLE 15]

2-(4-Fluorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

15 Following a procedure similar to that described in Example 13-3), but using methacrolein instead of acrolein, the title compound was obtained as a pale yellow powder (yield 24%), melting at 168 - 170°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.85 (2H, doublet, J = 9 Hz); 7.21 (2H, doublet, J = 9 Hz); 7.12 - 7.03 (2H, multiplet); 7.00 -
20 6.89 (2H, multiplet); 6.74 (1H, singlet); 6.27 (1H, singlet); 4.82 (2H, singlet); 2.18 (3H, singlet).

Mass spectrum (EI) m/z: 330 [M⁺].

[EXAMPLE 16]

25 2-(4-Methylphenyl)-1-(4-sulfamoylphenyl)pyrrole

1) N-(4-Methylbenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 4-methylbenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a white powder (yield 91%).

30 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.60 (1H, singlet); 7.90 - 7.81 (4H, multiplet); 7.42 - 7.32 (4H, multiplet); 2.40 (3H, singlet).

2) 4-Methyl- α -(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-methylbenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a white powder (yield 94%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.70 (2H, doublet, $J = 9$ Hz); 7.48 (2H, doublet, $J = 9$ Hz); 7.26 (2H, doublet, $J = 9$ Hz); 6.68 (1H, doublet, $J = 8$ Hz); 6.84 (2H, doublet, $J = 9$ Hz); 6.72 (2H, singlet); 5.67 (1H, doublet, $J = 8$ Hz); 2.38 (3H, singlet).

3) 2-(4-Methylphenyl)-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 4-methyl- α -(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and acrolein as starting materials, the title compound was obtained as a brown powder (yield 13%), melting at 183 - 184°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.87 (2H, doublet, $J = 9$ Hz); 7.28 (2H, doublet, $J = 9$ Hz); 7.09 - 6.98 (4H, multiplet); 6.96 - 6.93 (1H, multiplet); 6.44 - 6.38 (2H, multiplet); 4.81 (2H, singlet); 2.33 (3H, singlet).

Mass spectrum (EI) m/z : 313 $[(M+H)^+]$.

[EXAMPLE 17]

3-Methyl-2-(4-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 16-3), but using crotonaldehyde instead of acrolein, the title compound was obtained as a brown amorphous material (yield 33%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.79 (2H, doublet, $J = 9$ Hz); 7.16 (2H, doublet, $J = 9$ Hz); 7.09 (2H, doublet, $J = 9$ Hz); 6.97 (2H, doublet, $J = 9$ Hz); 6.89 (1H, doublet, $J = 3$ Hz); 6.28 (1H, doublet, $J = 3$ Hz); 4.83 (2H, singlet); 2.34 (3H, singlet); 2.15 (3H, singlet).

Mass spectrum (EI) m/z : 326 $[M^+]$.

[EXAMPLE 18]

4-Methyl-2-(4-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 16-3), but using methacrolein instead of acrolein as starting materials, the title compound was obtained as a pale brown powder (yield 5%), melting at 175 - 176°C.

5 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.84 (2H, doublet, J = 9 Hz); 7.23 (2H, doublet, J = 9 Hz); 7.08-6.97 (4H, multiplet); 6.73 (1H, doublet, J = 2 Hz); 6.27 (1H, doublet, J = 2 Hz); 4.79 (2H, singlet); 2.32 (2H, singlet); 2.18 (2H, singlet).

10 [EXAMPLE 19]

1-(4-Fluorophenyl)-2-(4-sulfamoylphenyl)pyrrole

1) 4-Fluoro-N-(4-sulfamoylbenzylidene)aniline

Following a procedure similar to that described in Example 1-1), but using 4-sulfamoylbenzaldehyde and 4-fluoroaniline as starting materials, the title compound was
15 obtained as white prismatic crystals (yield 25%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.74 (1H, singlet); 8.11 (2H, doublet, J = 8 Hz); 7.96 (2H, doublet, J = 8 Hz); 7.50 (2H, singlet); 7.43 - 7.25 (4H, multiplet).

20 2) α-(4-Fluoroanilino)-4-sulfamoylphenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using 4-fluoro-N-(4-sulfamoylbenzylidene)aniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a slightly yellow powder (yield 83%).

25 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.93 (2H, doublet, J = 8 Hz); 7.76 (2H, doublet, J = 8 Hz); 7.45 (2H, singlet); 7.05 (2H, triplet, J = 9 Hz); 6.73 - 6.85 (3H, multiplet); 6.12 (1H, doublet, J = 10 Hz).

Mass spectrum (EI) m/z: 279 [M⁺].

30 3) 1-(4-Fluorophenyl)-2-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using α-(4-fluoroanilino)-4-sulfamoylphenylacetonitrile [prepared as described in step 2)] and acrolein

as starting materials, the title compound was obtained as a white powder (yield 48%), melting at 160 - 161°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

- 5 7.67 (2H, doublet, $J = 8$ Hz); 7.32 - 7.22 (8H, multiplet); 7.14 (1H, triplet, $J = 2$ Hz); 6.59 (1H, doublet of doublets, $J = 4$ & 2 Hz); 6.36 (1H, triplet, $J = 3$ Hz).

Mass spectrum (EI) m/z : 316 [M^+].

[EXAMPLE 20]

10 1-(4-Fluorophenyl)-4-methyl-2-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 19-3), but using methacrolein instead of acrolein, the title compound was obtained as a white powder (yield 62%), melting at 126 - 127°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, $CDCl_3$) δ ppm:

- 15 7.87 (2H, doublet, $J = 9$ Hz); 7.39 - 7.17 (6H, multiplet); 6.87 (1H, singlet); 6.53 (1H, singlet); 4.93 (2H, singlet); 2.31 (3H, singlet).

Mass spectrum (EI) m/z : 330 [M^+].

[EXAMPLE 21]

20 2-(4-Fluorophenyl)-3-methyl-1-(4-methylsulfonylphenyl)pyrrole

1) N-(4-Fluorobenzylidene)-4-methylthioaniline

Following a procedure similar to that described in Example 1-1), but using 4-fluorobenzaldehyde and 4-methylthioaniline as starting materials, the title compound was obtained as a pale yellow needle-like crystals (yield 87%).

25 Nuclear Magnetic Resonance Spectrum (270 MHz, $CDCl_3$) δ ppm:

8.43 (1H, singlet); 7.94 - 7.86 (2H, multiplet); 7.33 - 7.27 (2H, multiplet); 7.21 - 7.12 (4H, multiplet); 2.52 (3H, singlet).

2) 4-Fluoro- α -(4-methylthioanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-fluorobenzylidene)-4-methylthioaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a pale yellow powder (yield 96%).

30

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.63 - 7.54 (2H, multiplet); 7.27 (2H, doublet, $J = 9$ Hz); 7.21 - 7.12 (2H, multiplet); 6.73 (2H, doublet, $J = 9$ Hz); 5.40 (1H, doublet, $J = 9$ Hz); 4.01 (1H, doublet, $J = 9$ Hz); 2.45 (3H, singlet).

5 3) 2-(4-Fluorophenyl)-3-methyl-1-(4-methylsulfonylphenyl)pyrrole

A solution of 2.00 g (7.3 mmol) of 4-fluoro- α -(4-methylthioanilino)phenylacetonitrile [prepared as described in step 2)] in 15 ml of tetrahydrofuran was cooled to -78°C under a stream of nitrogen, and 0.67 ml (8.1 mmol) of crotonaldehyde was added to the resulting solution. 8.10 ml (8.1 mmol) of a 1.0 M solution of lithium bis(trimethylsilyl)amide were then added dropwise to the mixture, and the resulting mixture was stirred at -78°C, after which the mixture was stirred overnight whilst allowing its temperature to rise naturally. The tetrahydrofuran was then removed by distillation under reduced pressure, and ethyl acetate was added to the residue. The resulting mixture was washed with a saturated aqueous solution of ammonium chloride, with water and with a saturated aqueous solution of sodium chloride, in that order. The organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was then removed by distillation under reduced pressure. The resulting residue was dissolved in 20 ml of dichloroethane, and 3.98 g (16.2 mmol) of 70% m-chloroperbenzoic acid were added to the resulting solution in several portions, whilst ice-cooling. The mixture was then stirred, whilst ice-cooling for 30 minutes. At the end of this time, the reaction mixture was diluted with methylene chloride and then washed with a 10% w/v aqueous solution of sodium thiosulfate and with a saturated aqueous solution of sodium hydrogencarbonate twice each, in that order. Thereafter, the organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was heated at 150°C for 2 hours, after which it was applied to a silica gel chromatography column and eluted, using a 2 : 1 by volume mixture of hexane and ethyl acetate as the eluent, to give 0.36 g (yield 15%) of the title compound as a white powder, melting at 157 - 158°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.83 (2H, doublet, $J = 9$ Hz); 7.20 (2H, doublet, $J = 9$ Hz); 7.10 - 6.95 (4H, multiplet); 6.91 (1H, doublet, $J = 3$ Hz); 6.30 (1H, doublet, $J = 3$ Hz); 3.06 (3H, singlet); 2.14 (3H, singlet).

Mass spectrum (EI) m/z : 329 [M^+].

[EXAMPLE 22]

2-(4-Fluorophenyl)-1-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 21-3), but using acrolein
5 instead of crotonaldehyde, the title compound was obtained as a white powder (yield 7%),
melting at 195 - 196°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.90 (2H, doublet, J = 9 Hz); 7.31 (2H, doublet, J = 9 Hz); 7.13 - 7.05 (2H, multiplet); 7.01 -
6.92 (3H, multiplet); 6.46 - 6.40 (2H, multiplet); 3.08 (3H, singlet).

10 Mass spectrum (EI) m/z: 315 [M⁺].

[EXAMPLE 23]

2-(4-Fluorophenyl)-4-methyl-1-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 21-3), but using
15 methacrolein instead of crotonaldehyde, the title compound was obtained as a white powder
(yield 36%), melting at 151 - 154°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.87 (2H, doublet, J = 9 Hz); 7.26 (2H, doublet, J = 9 Hz); 7.12 - 7.03 (2H, multiplet); 7.00 -
6.92 (2H, multiplet); 6.76 (1H, doublet, J = 2 Hz); 6.28 (1H, doublet, J = 2 Hz); 3.08 (3H,
20 singlet); 2.18 (3H, singlet).

Mass spectrum (EI) m/z: 329 [M⁺].

[EXAMPLE 24]

3-Ethyl-2-(4-fluorophenyl)-1-(4-methylsulfonylphenyl)pyrrole

25 Following a procedure similar to that described in Example 21-3), but using 2-pentenal
instead of crotonaldehyde, the title compound was obtained as a white powder (yield 15%),
melting at 107 - 108°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.82 (2H, doublet, J = 9 Hz); 7.21 - 6.93 (7H, multiplet); 6.36 (1H, doublet, J = 3 Hz); 3.05
30 (3H, singlet); 2.50 (2H, quartet, J = 8 Hz); 1.19 (3H, triplet, J = 8 Hz).

Mass spectrum (EI) m/z: 343 [M⁺].

[EXAMPLE 25]

2-(4-Fluorophenyl)-1-(4-methylsulfonylphenyl)-3-propylpyrrole

Following a procedure similar to that described in Example 21-3), but using 2-hexenal
5 instead of crotonaldehyde, the title compound was obtained as white prismatic crystals (yield 20%), melting at 116 - 117°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.82 (2H, doublet, J = 9 Hz); 7.19 (2H, doublet, J = 9 Hz); 7.06 - 6.92 (5H, multiplet); 6.33
(1H, doublet, J = 3 Hz); 3.05 (3H, singlet); 2.44 (2H, triplet, J = 8 Hz); 1.63 - 1.56 (2H,
10 multiplet); 0.92 (3H, triplet, J = 7 Hz).

Mass spectrum (EI) m/z: 357 [M⁺].

[EXAMPLE 26]

2-(4-Chlorophenyl)-1-(4-methylsulfonylphenyl)pyrrole

15 1) N-(4-Chlorobenzylidene)-4-methylthioaniline

Following a procedure similar to that described in Example 1-1), but using 4-chlorobenzaldehyde and 4-methylthioaniline as starting materials, the title compound was obtained as pale yellow needle-like crystals (yield 94%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

20 8.43 (1H, singlet); 7.83 (2H, doublet, J = 9 Hz); 7.45 (2H, doublet, J = 9 Hz); 7.30 (2H, doublet, J = 9 Hz); 7.18 (2H, doublet, J = 9 Hz); 2.51 (3H, singlet).

2) 4-Chloro-α-(4-methylthioanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-chlorobenzylidene)-4-methylthioaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a pale yellow powder (yield
25 84%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.55 (2H, doublet, J = 9 Hz); 7.44 (2H, doublet, J = 9 Hz); 7.27 (2H, doublet, J = 9 Hz); 6.72
(2H, doublet, J = 9 Hz); 5.40 (1H, doublet, J = 9 Hz); 4.02 (1H, doublet, J = 9 Hz); 2.45 (3H,
30 singlet).

3) 2-(4-Chlorophenyl)-1-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 21-3), but using 4-chloro- α -(4-methylthioanilino)phenylacetonitrile [prepared as described in step 2)] and acrolein as starting materials, the title compound was obtained as an orange-colored powder (yield 32%), melting at 203 - 205°C.

5 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.91 (2H, doublet, $J = 9$ Hz); 7.32 (2H, doublet, $J = 9$ Hz); 7.23 (2H, doublet, $J = 9$ Hz); 7.05 (2H, doublet, $J = 9$ Hz); 7.00 - 6.97 (1H, multiplet); 6.48 - 6.45 (1H, multiplet); 6.44 - 6.40 (1H, multiplet); 3.09 (3H, singlet).

Mass spectrum (EI) m/z : 331 [M^+].

10

[EXAMPLE 27]

2-(4-Chlorophenyl)-3-methyl-1-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 26-3), but using crotonaldehyde instead of acrolein, the title compound was obtained as a pale yellow powder (yield 21%), melting at 173 - 174°C.

15

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.84 (2H, doublet, $J = 9$ Hz); 7.27 (2H, doublet, $J = 9$ Hz); 7.21 (2H, doublet, $J = 9$ Hz); 7.01 (2H, doublet, $J = 9$ Hz); 6.92 (1H, doublet, $J = 3$ Hz); 6.30 (1H, doublet, $J = 3$ Hz); 3.07 (3H, singlet); 2.15 (3H, singlet).

20

Mass spectrum (EI) m/z : 345 [M^+].

[EXAMPLE 28]

2-(4-Methoxyphenyl)-1-(4-methylsulfonylphenyl)pyrrole

1) N-(4-Methoxybenzylidene)-4-methylthioaniline

25

Following a procedure similar to that described in Example 1-1), but using 4-methoxybenzaldehyde and 4-methylthioaniline as starting materials, the title compound was obtained as a slightly yellow powder (yield 100%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

8.39 (1H, singlet); 7.84 (2H, doublet, $J = 9$ Hz); 7.29 (2H, doublet, $J = 9$ Hz); 7.16 (2H, doublet, $J = 9$ Hz); 6.98 (2H, doublet, $J = 9$ Hz); 3.88 (3H, singlet); 2.51 (3H, singlet).

30

2) 4-Methoxy- α -(4-methylthioanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-methoxybenzylidene)-4-methylthioaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a pale brown powder (yield 92%).

5 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.47 (2H, doublet, J = 9 Hz); 7.27 (2H, doublet, J = 9 Hz); 6.97 (2H, doublet, J = 9 Hz); 6.73 (2H, doublet, J = 9 Hz); 5.34 (1H, doublet, J = 9 Hz); 3.97 (1H, doublet, J = 9 Hz); 3.84 (3H, singlet); 2.45 (3H, singlet).

3) 2-(4-Methoxyphenyl)-1-(4-methylsulfonylphenyl)pyrrole

10 Following a procedure similar to that described in Example 21-3), but using 4-methoxy- α -(4-methylthioanilino)phenylacetonitrile [prepared as described in step 2)] and acrolein as starting materials, the title compound was obtained as a white powder (yield 9%), melting at 183 - 184°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

15 7.88 (2H, doublet, J = 9 Hz); 7.32 (2H, doublet, J = 9 Hz); 7.05 (2H, doublet, J = 9 Hz); 7.98 - 7.93 (1H, multiplet); 6.80 (2H, doublet, J = 9 Hz); 6.43 - 6.37 (2H, multiplet); 3.80 (3H, singlet); 3.08 (3H, singlet).

Mass spectrum (EI) m/z: 327 [M⁺].

20 [EXAMPLE 29]

2-(4-Methylphenyl)-1-(4-methylsulfonylphenyl)pyrrole

1) N-(4-Methylbenzylidene)-4-methylthioaniline

25 Following a procedure similar to that described in Example 1-1), but using 4-methylbenzaldehyde and 4-methylthioaniline as starting materials, the title compound was obtained as a slightly yellow powder (yield 96%).

Mass spectrum (EI) m/z: 241 [M⁺].

2) 4-Methyl- α -(4-methylthioanilino)phenylacetonitrile

30 Following a procedure similar to that described in Example 1-2), but using N-(4-methylbenzylidene)-4-methylthioaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a pale yellow powder (yield 73%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.47 (2H, doublet, J = 9 Hz); 7.27 (4H, doublet, J = 9 Hz); 6.73 (2H, doublet, J = 9 Hz); 5.36 (1H, doublet, J = 8 Hz); 3.99 (1H, doublet, J = 8 Hz); 2.44 (3H, singlet); 2.40 (3H, singlet).

3) 2-(4-Methylphenyl)-1-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 21-3), but using 4-methyl-
5 α -(4-methylthioanilino)phenylacetonitrile [prepared as described in step 2)] and acrolein as starting materials, the title compound was obtained as a yellow powder (yield 16%), melting at 186 - 187°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.88 (2H, doublet, J = 9 Hz); 7.32 (2H, doublet, J = 9 Hz); 7.10 - 6.94 (5H, multiplet); 6.45 -
10 6.39 (2H, multiplet); 3.08 (3H, singlet); 2.33 (3H, singlet).

Mass spectrum (EI) m/z: 311 [M⁺].

[EXAMPLE 30]

2-(4-Methoxyphenyl)-3-methyl-1-(4-methylsulfonylphenyl)pyrrole

15 1) 4-Methoxy- α -(4-methylsulfonylanilino)phenylacetonitrile

6.41 g (20.3 mmol) of 4-methoxy- α -(4-methylthioanilino)phenylacetonitrile [prepared as described in Example 28-2)] were dissolved in 160 ml of dichloroethane, and 12.23 g (49.8 mmol) of 70% m-chloroperbenzoic acid were added to the resulting solution in several portions, whilst ice-cooling. The mixture was then stirred for 30 minutes, after which the
20 reaction mixture was diluted with methylene chloride and then washed once with a 10% w/v aqueous solution of sodium thiosulfate and once with a saturated aqueous solution of sodium hydrogencarbonate, in that order; the two washings were then repeated in the same order. The organic layer was separated and dried over anhydrous magnesium sulfate and the solvent was then removed by distillation under reduced pressure. The resulting residue was applied
25 to a silica gel chromatography column and eluted with a 1 : 2 by volume mixture of ethyl acetate and hexane, to give 3.65 g of 4-methoxy- α -(4-methylsulfonylanilino)phenylacetonitrile as a pale yellow powder (yield 51%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.83 (2H, doublet, J = 9 Hz); 7.50 (2H, doublet, J = 9 Hz); 6.99 (2H, doublet, J = 9 Hz); 6.83
30 (2H, doublet, J = 9 Hz); 5.43 (1H, doublet, J = 8 Hz); 4.56 (1H, doublet, J = 8 Hz); 3.85 (3H, singlet); 3.03 (3H, singlet).

2) 2-(4-Methoxyphenyl)-3-methyl-1-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 4-methoxy- α -(4-methylsulfonylanilino)phenylacetonitrile [prepared as described in step 1)] and crotonaldehyde as starting materials, the title compound was obtained as an orange-colored powder (yield 40%), melting at 131 - 132°C.

5 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.81 (2H, doublet, J = 9 Hz); 7.21 (2H, doublet, J = 9 Hz); 7.01 (2H, doublet, J = 9 Hz); 6.89 (1H, doublet, J = 3 Hz); 6.84 (1H, doublet, J = 3 Hz); 6.29 (1H, doublet, J = 3 Hz); 3.81 (3H, singlet); 3.05 (3H, singlet); 2.14 (3H, singlet).

Mass spectrum (EI) m/z: 341 [M⁺].

10

[EXAMPLE 31]

3-Methyl-2-(4-methylphenyl)-1-(4-methylsulfonylphenyl)pyrrole

1) 4-Methyl- α -(4-methylsulfonylanilino)phenylacetonitrile

15 Following a procedure similar to that described in Example 30-1), but using 4-methyl- α -(4-methylthioanilino)phenylacetonitrile [prepared as described in Example 29-2)] and m-chloroperbenzoic acid as starting materials, the title compound was obtained as a white powder (yield 93%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

20 7.83 (2H, doublet, J = 9 Hz); 7.47 (2H, doublet, J = 9 Hz); 7.30 (2H, doublet, J = 9 Hz); 6.84 (2H, doublet, J = 9 Hz); 5.45 (1H, doublet, J = 8 Hz); 4.55 (1H, doublet, J = 8 Hz); 3.03 (3H, singlet); 2.41 (3H, singlet).

2) 3-Methyl-2-(4-methylphenyl)-1-(4-methylsulfonylphenyl)pyrrole

25 Following a procedure similar to that described in Example 1-3), but using 4-methyl- α -(4-methylsulfonylanilino)phenylacetonitrile [prepared as described in step 1)] and crotonaldehyde as starting materials, the title compound was obtained as a pale brown powder (yield 46%), melting at 158 - 160°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

30 7.81 (2H, doublet, J = 9 Hz); 7.21 (2H, doublet, J = 9 Hz); 7.10 (2H, doublet, J = 9 Hz); 6.97 (2H, doublet, J = 9 Hz); 6.90 (1H, doublet, J = 3 Hz); 6.29 (1H, doublet, J = 3 Hz); 3.05 (3H, singlet); 2.35 (3H, singlet); 2.15 (3H, singlet).

Mass spectrum (FAB) m/z: 326 [(M+H)⁺].

[EXAMPLE 32]

2-(4-Difluoromethoxyphenyl)-3-methyl-1-(4-methylsulfonylphenyl)pyrrole

1) 4-Difluoromethoxy- α -(4-methylthioanilino)phenylacetonitrile

5 Following a procedure similar to that described in Example 1-1), but using 4-difluoromethoxybenzaldehyde and 4-methylthioaniline as starting materials, N-(4-difluoromethoxybenzylidene)-4-methylthioaniline was obtained in a yield of 91%. This aniline compound and trimethylsilyl cyanide were then reacted together in a similar manner to that described in Example 1-2), to give the title compound as a slightly yellow powder
10 (yield 80%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.61 (2H, doublet, J = 9 Hz); 7.27 (2H, doublet, J = 9 Hz); 7.22 (2H, doublet, J = 9 Hz); 6.73 (2H, doublet, J = 9 Hz); 6.56 (1H, triplet, J = 73 Hz); 5.41 (1H, doublet, J = 9 Hz); 4.01 (1H, doublet, J = 9 Hz); 2.45 (3H, singlet).

15 2) 4-Difluoromethoxy- α -(4-methylsulfonylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 30-1), but using 4-difluoromethoxy- α -(4-methylthioanilino)phenylacetonitrile [prepared as described in step 1)] and m-chloroperbenzoic acid as starting materials, the title compound was obtained as a pale yellow powder (yield 89%).

20 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.84 (2H, doublet, J = 9 Hz); 7.61 (2H, doublet, J = 9 Hz); 7.25 (2H, doublet, J = 9 Hz); 6.84 (2H, doublet, J = 9 Hz); 6.57 (1H, triplet, J = 73 Hz); 5.51 (1H, doublet, J = 8 Hz); 4.60 (1H, doublet, J = 8 Hz); 3.03 (3H, singlet).

3) 2-(4-Difluoromethoxyphenyl)-3-methyl-1-(4-methylsulfonylphenyl)pyrrole

25 Following a procedure similar to that described in Example 1-3), but using 4-difluoromethoxy- α -(4-methylsulfonylanilino)phenylacetonitrile [prepared as described in step 2)] and crotonaldehyde as starting materials, the title compound was obtained as a white powder (yield 31%), melting at 98 - 99°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

30 7.83 (2H, doublet, J = 9 Hz); 7.21 (2H, doublet, J = 9 Hz); 7.12 - 7.02 (4H, multiplet); 6.91 (1H, doublet, J = 3 Hz); 6.54 (1H, triplet, J = 74 Hz); 6.30 (1H, doublet, J = 3 Hz); 3.06 (3H, singlet); 2.15 (3H, singlet).

Mass spectrum (EI) m/z: 377 [M⁺].

[EXAMPLE 33]

1-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

5 1) α -(4-Fluoroanilino)-4-methylthiophenylacetonitrile

Following a procedure similar to that described in Example 1-1), but using 4-methylthiobenzaldehyde and 4-fluoroaniline as starting materials, 4-fluoro-N-(4-methylthiobenzylidene)aniline was obtained in a yield of 89%. This compound and trimethylsilyl cyanide were then reacted together in a similar manner to that described in
10 Example 1-2), to give the title compound as a slightly yellow powder (yield 47%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.50 (2H, doublet, J = 9 Hz); 7.31 (2H, doublet, J = 9 Hz); 6.98 (2H, triplet, J = 9 Hz); 6.73 (2H, doublet of doublets, J = 9 & 4 Hz); 5.33 (1H, doublet, J = 9 Hz); 3.92 (1H, doublet, J = 9 Hz); 2.51 (3H, singlet).

15 2) 1-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 21-3), but using α -(4-fluoroanilino)-4-methylthiophenylacetonitrile [prepared as described in step 1)] and acrolein as starting materials, the title compound was obtained as a yellow powder (yield 7%), melting at 145 - 147°C.

20 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.77 (2H, doublet, J = 9 Hz); 7.27 (2H, doublet, J = 9 Hz); 7.18 - 7.04 (4H, multiplet); 6.96 (1H, doublet of doublets, J = 3 & 2 Hz); 6.58 (1H, doublet of doublets, J = 4 & 2 Hz); 6.40 (1H, doublet of doublets, J = 4 & 3 Hz); 3.04 (3H, singlet).

Mass spectrum (EI) m/z: 315 [M⁺].

25

[EXAMPLE 34]

1-(4-Fluorophenyl)-4-methyl-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 33-2), but using methacrolein instead of acrolein, the title compound was obtained as a white powder (yield
30 4%), melting at 127 - 130°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.75 (2H, doublet, $J = 9$ Hz); 7.24 (2H, doublet, $J = 9$ Hz); 7.15 - 7.03 (4H, multiplet); 6.74 (1H, doublet, $J = 2$ Hz); 6.42 (1H, doublet, $J = 2$ Hz); 3.04 (3H, singlet); 2.18 (3H, singlet).
Mass spectrum (EI) m/z : 329 [M^+].

5 [EXAMPLE 35]

5-Bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

0.32 g (1.0 mmol) of 1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole (prepared as described in Example 33) was dissolved in 10 ml of anhydrous tetrahydrofuran, and 0.18 g (1.0 mmol) of *N*-bromosuccinimide was added to the resulting solution, whilst ice-cooling.

10 The mixture was then stirred, whilst ice-cooling for 1 hour and then at room temperature for a further 1 hour. At the end of this time, water was added to the mixture, and the resulting mixture was extracted with methylene chloride. The organic extract was dried over anhydrous magnesium sulfate, and the solvent was then removed by distillation under reduced pressure. The resulting residue was applied to a silica gel chromatography column
15 and eluted with a 1 : 3 by volume mixture of ethyl acetate and hexane, to give 0.28 g of 5-Bromo-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole as a white powder (yield 70%), melting at 174 - 176°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, $CDCl_3$) δ ppm:

7.73 (2H, doublet, $J = 9$ Hz); 7.23 - 7.09 (6H, multiplet); 6.57 (1H, doublet, $J = 4$ Hz); 6.44
20 (1H, doublet, $J = 4$ Hz); 3.02 (3H, singlet).

Mass spectrum (EI) m/z : 393 [M^+].

[EXAMPLE 36]

5-Bromo-1-(4-fluorophenyl)-4-methyl-2-(4-methylsulfonylphenyl)pyrrole

25 Following a procedure similar to that described in Example 35, but using 1-(4-fluorophenyl)-4-methyl-2-(4-methylsulfonylphenyl)pyrrole (prepared as described in Example 34) and *N*-bromosuccinimide as starting materials, the title compound was obtained as a white powder (yield 30%), melting at 158 - 159°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, $CDCl_3$) δ ppm:

30 7.71 (2H, doublet, $J = 9$ Hz); 7.19 - 7.11 (6H, multiplet); 6.49 (1H, singlet); 3.02 (3H, singlet); 2.15 (3H, singlet).

Mass spectrum (EI) m/z : 407 [M^+].

[EXAMPLE 37]

5-Chloro-1-(4-fluorophenyl)-4-methyl-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 35, but using N-chlorosuccinimide instead of N-bromosuccinimide, the title compound was obtained as a white powder (yield 58%), melting at 151 - 154°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.71 (2H, doublet, J = 9 Hz); 7.20 - 7.05 (6H, multiplet); 6.44 (1H, singlet); 3.02 (3H, singlet).

Mass spectrum (EI) m/z: 363 [M⁺].

[EXAMPLE 38]

5-Chloro-1-(4-fluorophenyl)-4-methyl-2-(4-sulfamoylphenyl)pyrrole

1-(4-Fluorophenyl)-4-methyl-2-(4-sulfamoylphenyl)pyrrole (prepared as described in Example 20) was chlorinated in the same manner as described in Example 37, to give the title compound as white prismatic crystals (yield 67%), melting at 119 - 120°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.63 (2H, doublet, J = 8 Hz); 7.33 - 7.17 (8H, multiplet); 6.55 (1H, singlet); 2.10 (3H, singlet).

Mass spectrum (EI) m/z: 364 [M⁺].

[EXAMPLE 39]

5-Chloro-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

1-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole (prepared as described in Example 33) was chlorinated in the same manner as described in Example 37, to give the title compound as a white powder (yield 86%), melting at 180 - 182°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.73 (2H, doublet, J = 9 Hz); 7.23 - 7.09 (6H, multiplet); 6.54 (1H, doublet, J = 4 Hz); 6.32 (1H, doublet, J = 4 Hz); 3.02 (3H, singlet).

Mass spectrum (EI) m/z: 349 [M⁺].

[EXAMPLE 40]

1-(4-Fluorophenyl)-5-iodo-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 35, but using N-iodosuccinimide instead of N-bromosuccinimide, the title compound was obtained as a yellow powder (yield 51%), melting at 174 - 176°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.73 (2H, doublet, J = 9 Hz); 7.22 - 7.12 (6H, multiplet); 6.63 (1H, doublet, J = 4 Hz); 6.59 (1H, doublet, J = 4 Hz); 3.02 (3H, singlet).

Mass spectrum (EI) m/z: 441 [M⁺].

[EXAMPLE 41]

5-Fluoro-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

0.90 g (2.7 mmol) of 1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole (prepared as described in Example 33) was dissolved in 10 ml of acetonitrile in a reaction vessel made of polyethylene, and 0.46 g (2.7 mmol) of xenon difluoride was added to the resulting solution at 0°C, whilst stirring. The temperature of the reaction mixture was then allowed to return to room temperature, and the mixture was stirred at room temperature for 20 hours. At the end of this time, 20 ml of a saturated aqueous solution of sodium carbonate was added to the mixture, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium carbonate and then with water, after which it was dried over anhydrous magnesium sulfate. The solvent was then removed by distillation under reduced pressure. The resulting residue was applied to a silica gel chromatography column and eluted with a 3 : 1 by volume mixture of hexane and ethyl acetate, to give 0.32 g of 5-fluoro-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole as white prismatic crystals (yield 34%), melting at 140 - 141°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.74 (2H, doublet, J = 9 Hz); 7.26 - 7.15 (6H, multiplet); 6.41 (1H, doublet of doublets, J = 6 & 4 Hz); 5.76 (1H, triplet, J = 4 Hz); 3.03 (3H, singlet).

Mass spectrum (EI) m/z: 333 [M⁺].

[EXAMPLE 42]

5-Fluoro-1-(4-fluorophenyl)-4-methyl-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 41, but using 1-(4-fluorophenyl)-4-methyl-2-(4-methylsulfonylphenyl)pyrrole (prepared as described in Example 34), 5-fluoro-1-(4-fluorophenyl)-4-methyl-2-(4-methylsulfonylphenyl)pyrrole was obtained as a white powder (yield 10%), melting at 109 - 110°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.71 (2H, doublet, J = 9 Hz); 7.19 - 7.10 (6H, multiplet); 6.30 (1H, doublet, J = 6 Hz); 3.02 (3H, singlet); 2.08 (3H, singlet).

Mass spectrum (EI) m/z: 347 [M⁺].

[EXAMPLE 43]

1-(4-Fluorophenyl)-5-methyl-2-(4-methylsulfonylphenyl)pyrrole

1) Methyl 2-(4-methylthiophenacyl)acetoacetate

2.28 g (19.7 mmol) of methyl acetoacetate were dissolved in 40 ml of 2-methyl-2-propanol, and 2.21 g (19.7 mmol) of potassium t-butoxide were added to the resulting solution under a nitrogen atmosphere. The mixture was then stirred at room temperature for 1 hour, after which a solution of 4.82 g (19.7 mmol) of 4-methylthiophenacyl bromide in 30 ml of benzene was added dropwise to the resulting mixture. The mixture was then stirred at 60°C for 3 hours, after which it was cooled. It was then poured into ice-water and extracted with ethyl acetate. The organic extract was washed with a saturated aqueous solution of sodium chloride, and then dried over anhydrous magnesium sulfate. The solvent was then removed by distillation under reduced pressure. The resulting residue was applied to a silica gel chromatography column and eluted with a 1 : 4 by volume mixture of ethyl acetate and hexane, to give 4.42 g (yield 80%) of methyl 2-(4-methylthiophenacyl)acetoacetate as a slightly yellow powder.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.89 (2H, doublet, J = 9 Hz); 7.27 (2H, doublet, J = 9 Hz); 4.23 (1H, doublet of doublets, J = 8 & 6 Hz); 3.78 (3H, singlet); 3.69 (1H, doublet of doublets, J = 18 & 8 Hz); 3.48 (1H, doublet of doublets, J = 18 & 6 Hz); 2.53 (3H, singlet); 2.44 (3H, singlet).

2) Methyl 2-(4-methylsulfonylphenacyl)acetoacetate

4.42 g (15.8 mmol) of methyl 2-(4-methylthiophenacyl)acetoacetate [prepared as described in step 1)] were dissolved in 150 ml of methylene chloride, and 7.77 g (31.5 mmol)

of 70 % *m*-chloroperbenzoic acid were added to the resulting solution, whilst ice-cooling. The mixture was then stirred at room temperature for 1 hour. 30 ml of a 10% w/v aqueous solution of sodium thiosulfate were added to the mixture, and the mixture was vigorously shaken, after which it separated into liquid phases. The organic layer was separated and washed with a saturated aqueous solution of sodium hydrogencarbonate and with a saturated aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous magnesium sulfate and the solvent was then removed by distillation under reduced pressure. The residue was applied to a silica gel chromatography column and eluted with a 1 : 1 by volume mixture of ethyl acetate and hexane, to give 3.65 g (yield 74%) of methyl 2-(4-methylsulfonylphenacyl)acetoacetate as a slightly yellow powder.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

8.16 (2H, doublet, *J* = 9 Hz); 8.07 (2H, doublet, *J* = 9 Hz); 4.26 (1H, doublet of doublets, *J* = 8 & 6 Hz); 3.80 (3H, singlet); 3.75 (1H, doublet of doublets, *J* = 19 & 8 Hz); 3.52 (1H, doublet of doublets, *J* = 19 & 6 Hz); 3.09 (3H, singlet); 2.46 (3H, singlet).

3) 1-(4-Fluorophenyl)-4-methoxycarbonyl-5-methyl-2-(4-methylsulfonylphenyl)pyrrole

3.00 g (9.6 mmol) of methyl 2-(4-methylsulfonylphenacyl)acetoacetate [prepared as described in step 2)] were dissolved in 100 ml of acetic acid and 0.97 g (8.7 mmol) of 4-fluoroaniline was added to the resulting solution. The resulting mixture was then heated under reflux for 5 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate was added to the residue and the mixture was extracted with ethyl acetate. The organic extract was washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous magnesium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was applied to a silica gel chromatography column and eluted with a 1 : 2 by volume mixture of ethyl acetate and hexane, to give 3.10 g of 1-(4-fluorophenyl)-4-methoxycarbonyl-5-methyl-2-(4-methylsulfonylphenyl)pyrrole as a white powder (yield 92%), melting at 154 - 155°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.73 (2H, doublet, *J* = 9 Hz); 7.21 - 7.12 (6H, multiplet); 6.94 (1H, singlet); 3.87 (3H, singlet); 3.02 (3H, singlet); 2.41 (3H, singlet).

Mass spectrum (EI) *m/z*: 387 [M⁺].

4) 1-(4-Fluorophenyl)-5-methyl-2-(4-methylsulfonylphenyl)pyrrole

1.00 g (2.6 mmol) of 1-(4-fluorophenyl)-4-methoxycarbonyl-5-methyl-2-(4-methylsulfonylphenyl)pyrrole [prepared as described in step 3)] was suspended in 20 ml of ethanol, and 2.5 ml of a 20% w/v aqueous solution of potassium hydroxide were added to the resulting suspension. The mixture was then heated under reflux for 15 hours. At the end of this time, the mixture was cooled, and diethyl ether was added. The mixture was then shaken and the liquid phases were separated. 3 N aqueous hydrochloric acid was added to the aqueous layer to make it acidic, and then the layer was extracted with ethyl acetate. The organic extract was washed with a saturated aqueous solution of sodium chloride, after which it was dried over anhydrous magnesium sulfate and the solvent was then removed by distillation under reduced pressure, to give 0.92 g of a carboxylic acid, a hydrolysed product.

0.92 g of this carboxylic acid was suspended in 12 ml of glycerol and the resulting suspension was stirred at 200°C for 30 minutes. At the end of this time, the reaction mixture was poured into ice-water and the resulting mixture was extracted with ethyl acetate. The organic extract was washed with a saturated aqueous solution of sodium chloride, after which it was dried over anhydrous magnesium sulfate and the solvent was then removed by distillation under reduced pressure. The residue was applied to a silica gel chromatography column and eluted with a 1 : 4 by volume mixture of ethyl acetate and hexane, to give 0.55 g (yield 65%) of 1-(4-fluorophenyl)-5-methyl-2-(4-methylsulfonylphenyl)pyrrole as a white powder, melting at 110 - 112°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.68 (2H, doublet, J = 9 Hz); 7.20 - 7.08 (6H, multiplet); 6.51 (1H, doublet, J = 4 Hz); 6.13 (1H, doublet, J = 4 Hz); 3.01 (3H, singlet); 2.13 (3H, singlet).

Mass spectrum (EI) m/z: 329 [M⁺].

[EXAMPLE 44]

5-Trifluoromethyl-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

1) Ethyl 4,4,4-trifluoro-2-(4-methylthiophenacyl)acetoacetate

Following a procedure similar to that described in Example 43-1), but using ethyl 4,4,4-trifluoroacetoacetate instead of methyl acetoacetate, the title compound was obtained as a slightly yellow powder (yield 30%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.87 (2H, doublet, $J = 9$ Hz); 7.28 (2H, doublet, $J = 9$ Hz); 4.54 (1H, doublet of doublets, $J = 10$ & 5 Hz); 4.26 (2H, quartet, $J = 7$ Hz); 3.84 (1H, doublet of doublets, $J = 18$ & 10 Hz); 3.68 (1H, doublet of doublets, $J = 18$ & 5 Hz); 2.53 (3H, singlet); 1.29 (3H, triplet, $J = 7$ Hz).

2) 5,5,5-Trifluoro-1-(4-methylthiophenyl)pentane-1,4-dione

5 1.65 g (4.7 mmol) of ethyl 4,4,4-trifluoro-2-(4-methylthiophenacyl)acetoacetate [prepared as described in step 1)] were dissolved in 15 ml of dimethylformamide, and 85 ml (4.7 mmol) of water and 0.20 g (4.7 mmol) of lithium chloride were added to the resulting solution. The mixture was then stirred at 140°C for 1 hour, after which it was poured into ice-water and the resulting mixture was extracted with ethyl acetate. The organic extract was
10 washed with water and dried over anhydrous magnesium sulfate, and the solvent was then removed by distillation under reduced pressure. The resulting residue was applied to a silica gel chromatography column and eluted with a 3 : 1 by volume mixture of hexane and ethyl acetate, to give 0.26 g (yield 20%) of 5,5,5-trifluoro-1-(4-methylthiophenyl)pentane-1,4-dione as a slightly yellow powder.

15 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.89 (2H, doublet, $J = 9$ Hz); 7.28 (2H, doublet, $J = 9$ Hz); 3.38 (2H, triplet, $J = 6$ Hz); 3.14 (2H, triplet, $J = 6$ Hz).

3) 5-Trifluoromethyl-1-(4-fluorophenyl)-2-(4-methylthiophenyl)pyrrole

Following a procedure similar to that described in Example 43-3), but using 5,5,5-trifluoro-1-(4-methylthiophenyl)pentane-1,4-dione [prepared as described in step 2)] and 4-fluoroaniline as starting materials, the title compound was obtained as a pale brown oily substance (yield 42%).
20

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.25 (8H, multiplet); 6.76 (1H, doublet, $J = 4$ Hz); 6.36 (1H, doublet, $J = 4$ Hz); 2.44 (3H, singlet).
25

4) 5-Trifluoromethyl-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

5-Trifluoromethyl-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole [prepared as described in step 3)] was oxidized in the same manner as described in Example 43-2), to give the title compound as a white powder (yield 69%), melting at 136 - 139°C.

30 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.87 (2H, doublet, $J = 9$ Hz); 7.30 - 7.22 (4H, multiplet); 7.15 - 7.06 (2H, multiplet); 6.81 (1H, doublet, $J = 4$ Hz); 6.52 (1H, doublet, $J = 4$ Hz); 3.03 (3H, singlet).

Mass spectrum (EI) m/z : 383 [M^+].

[EXAMPLE 45]

1-(4-Fluorophenyl)-4,5-dimethyl-2-(4-methylsulfonylphenyl)pyrrole

5 1) Methyl 2-methyl-2-(4-methylsulfonylphenacyl)acetoacetate

0.65 g (2.1 mmol) of methyl 2-(4-methylsulfonylphenacyl)acetoacetate [prepared as described in Example 43-2)] was dissolved in 20 ml of anhydrous tetrahydrofuran, and 92 mg (2.3 mmol) of sodium hydride (as a 60% w/w dispersion in mineral oil) were added to the resulting solution, whilst ice-cooling and under a nitrogen atmosphere. The mixture was
10 stirred for 10 minutes, after which 1.1 ml (2.5 mmol) of methyl iodide were added, whilst ice-cooling, and the mixture was stirred for 2 hours. At the end of this time, water was added to the mixture, which was then extracted with ethyl acetate. The organic extract was washed with a saturated aqueous solution of sodium chloride, after which it was dried over anhydrous magnesium sulfate and the solvent was removed by distillation under reduced pressure. The
15 residue was applied to a silica gel chromatography column and eluted with a 2 : 3 by volume mixture of ethyl acetate and hexane, to give 0.54 g (yield 80%) of methyl 2-methyl-2-(4-methylsulfonylphenacyl)acetoacetate as a slightly yellow powder.

Nuclear Magnetic Resonance Spectrum (270 MHz, $CDCl_3$) δ ppm:

8.14 (2H, doublet, $J = 9$ Hz); 8.06 (2H, doublet, $J = 9$ Hz); 3.77 (3H, singlet); 3.69 (1H,
20 doublet, $J = 18$ Hz); 3.58 (1H, doublet, $J = 18$ Hz); 3.08 (3H, singlet); 2.35 (3H, singlet); 1.60 (3H, singlet).

2) 1-(4-Fluorophenyl)-4,5-dimethyl-2-(4-methylsulfonylphenyl)pyrrole

Hydrolysis and decarboxylation of methyl 2-methyl-2-(4-methylsulfonylphenacyl)acetoacetate [prepared as described in step 1)] were carried out to
25 give 3-methyl-1-(4-methylsulfonylphenyl)pentane-1,4-dione. This compound and 4-fluoroaniline were then reacted in the same manner as described in Example 43-3), to give the title compound as a yellow powder (yield 11%), melting at 159 - 162°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, $CDCl_3$) δ ppm:

7.67 (2H, doublet, $J = 9$ Hz); 7.18 - 7.09 (6H, multiplet); 6.41 (1H, singlet); 3.01 (3H,
30 singlet); 2.12 (3H, singlet); 2.04 (3H, singlet).

Mass spectrum (FAB) 344 [$(M+H)^+$]

[EXAMPLE 46]

1-(4-Fluorophenyl)-4-hydroxymethyl-2-(4-methylsulfonylphenyl)pyrrole

1) Methyl 2-(4-methylthiophenacyl)cyanoacetate

5 5.70 g (57.6 mmol) of methyl cyanoacetate were dissolved in 150 ml of anhydrous tetrahydrofuran, and 7.10 g (63.3 mmol) of potassium t-butoxide were added to the resulting solution, whilst ice-cooling, and the mixture was then stirred for 30 minutes. At the end of this time, a solution of 14.11 g (57.6 mmol) of 4-methylthiophenacyl bromide in 50 ml of tetrahydrofuran was slowly added dropwise to the mixture, whilst ice-cooling. The mixture
10 was stirred, whilst ice-cooling for 2 hours, and then a saturated aqueous solution of ammonium chloride and ethyl acetate were added. The insolubles were then filtered off. Water was added to the filtrate, and the mixture was extracted with ethyl acetate. The organic extract was dried over anhydrous magnesium sulfate and the solvent was then removed by distillation under reduced pressure. The residue was applied to a silica gel
15 chromatography column and eluted with a 1 : 2 by volume mixture of ethyl acetate and hexane, to give 3.11 g (yield 21%) of methyl 2-(4-methylthiophenacyl)cyanoacetate as a slightly yellow powder.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.87 (2H, doublet, J = 9 Hz); 7.27 (2H, doublet, J = 9 Hz); 4.16 (1H, doublet, J = 7 & 6 Hz);
20 3.83 (3H, singlet); 3.74 (1H, doublet, J = 18 & 7 Hz); 3.53 (1H, doublet, J = 18 & 6 Hz);
2.54 (3H, singlet).

2) 5-Amino-1-(4-fluorophenyl)-4-methoxycarbonyl-2-(4-methylsulfonylphenyl)pyrrole

3.11 g (11.8 mmol) of methyl 2-(4-methylthiophenacyl)cyanoacetate [prepared as described in step 1)] were dissolved in 150 ml of methylene chloride, and 5.83 g (23.6 mmol)
25 of 70% m-chloroperbenzoic acid were added to the mixture, whilst ice-cooling. The resulting mixture was then stirred at room temperature for 1 hour. At the end of this time, 50 ml of a 10% w/v aqueous solution of sodium thiosulfate were added to the mixture and the mixture was vigorously shaken, after which it was separated into liquid phases. The organic phase was washed with a saturated aqueous solution of sodium hydrogencarbonate and with a
30 saturated aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous magnesium sulfate and the solvent was removed by distillation under reduced

pressure, to give 3.15 g of methyl 2-(4-methylsulfonylphenacyl) cyanoacetate as a pale brown powder.

3.15 g of the powder thus obtained were dissolved in 100 ml of ethanol, and 1.58 g (14.2 mmol) of 4-fluoroaniline and 12 drops of concentrated aqueous hydrochloric acid were added to the resulting solution. The mixture was then heated under reflux for 3 days. At the end of this time, the reaction mixture was concentrated by evaporation under reduced pressure, methylene chloride was added to the residue, and then the insolubles were filtered off. The filtrate was concentrated by evaporation under reduced pressure, and the residue was applied to a silica gel chromatography column and eluted with a 1 : 1 by volume mixture of ethyl acetate and hexane, to give 2.10 g (yield 46%) of 5-amino-1-(4-fluorophenyl)-4-methoxycarbonyl-2-(4-methylsulfonylphenyl)pyrrole as a white powder.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.68 (2H, doublet, $J = 9$ Hz); 7.26 - 7.11 (6H, multiplet); 6.76 (1H, singlet); 5.15 (2H, broad singlet); 3.85 (3H, singlet); 3.01 (3H, singlet).

3) 1-(4-Fluorophenyl)-4-methoxycarbonyl-2-(4-methylsulfonylphenyl)pyrrole

2.00 g (5.2 mmol) of 5-amino-1-(4-fluorophenyl)-4-methoxycarbonyl-2-(4-methylsulfonylphenyl)pyrrole [prepared as described in step 2)] were dissolved in 50 ml of anhydrous tetrahydrofuran, and 6.38 g (61.8 mmol) of t-butyl nitrite were added to the resulting solution at room temperature and under a nitrogen atmosphere. The mixture was then stirred at room temperature for 30 minutes, after which it was heated under reflux for 2 hours. The solvent was then removed by distillation under reduced pressure and the residue was applied to a silica gel chromatography column and eluted with a 2 : 3 by volume mixture of ethyl acetate and hexane, to give 1.30 g (yield 68%) of 1-(4-fluorophenyl)-4-methoxycarbonyl-2-(4-methylsulfonylphenyl)pyrrole as a yellow powder, melting at 144 - 146°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.95 (2H, doublet, $J = 9$ Hz); 7.56 (1H, doublet, $J = 2$ Hz); 7.27 (1H, doublet, $J = 9$ Hz); 7.21 - 7.06 (4H, multiplet); 6.96 (1H, doublet, $J = 2$ Hz); 3.87 (3H, singlet); 3.05 (3H, singlet).

Mass spectrum (EI) m/z : 373 [M^+].

4) 1-(4-Fluorophenyl)-4-hydroxymethyl-2-(4-methylsulfonylphenyl)pyrrole

0.15 g (4.0 mmol) of lithium aluminum hydride was suspended in 25 ml of diethyl ether, and a solution of 0.98 g (2.6 mmol) of 1-(4-fluorophenyl)-4-methoxycarbonyl-2-(4-methylsulfonylphenyl)pyrrole [prepared as described in step 3)] in 20 ml of methylene chloride was added dropwise to the suspension whilst it was heated under reflux in a nitrogen atmosphere. The mixture was stirred under reflux for 1 hour, and then 0.15 ml of water, 0.15 ml of a 15% w/v aqueous solution of sodium hydroxide and 0.45 ml of water were added to the mixture, in that order. The mixture was then stirred at room temperature for 30 minutes. At the end of this time, the mixture was dehydrated by adding anhydrous magnesium sulfate, and it was filtered over a Celite (trade mark) filter aid. The solvent was then removed from the filtrate by distillation under reduced pressure. The residue was applied to a silica gel chromatography column and eluted with a 2 : 1 by volume mixture of ethyl acetate and hexane, to give 0.69 g (yield 76%) of 1-(4-fluorophenyl)-4-hydroxymethyl-2-(4-methylsulfonylphenyl)pyrrole as a white powder, melting at 88 - 90°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.77 (2H, doublet, J = 9 Hz); 7.26 (2H, doublet, J = 9 Hz); 7.28 - 7.05 (4H, multiplet); 6.97 (1H, doublet, J = 2 Hz); 6.60 (1H, doublet, J = 2 Hz); 4.65 (2H, doublet, J = 5 Hz); 3.04 (2H, singlet).

[EXAMPLE 47]

1-(4-Fluorophenyl)-4-hydroxymethyl-5-methyl-2-(4-methylsulfonylphenyl)pyrrole

1-(4-Fluorophenyl)-4-methoxycarbonyl-5-methyl-2-(4-methylsulfonylphenyl)pyrrole [prepared as described in Example 43-3)] was reduced in the same manner as described in Example 46-4), to give the title compound as a yellow powder (yield 84%), melting at 140 - 142°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.69 (2H, doublet, J = 9 Hz); 7.20 - 7.12 (6H, multiplet); 6.58 (1H, singlet); 4.63 (2H, doublet, J = 5 Hz); 3.01 (3H, singlet); 2.13 (3H, singlet).

Mass spectrum (FAB) m/z: 360 [(M+H)⁺].

[EXAMPLE 48]

5-Difluoromethyl-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

1) 1-(4-Fluorophenyl)-5-formyl-2-(4-methylsulfonylphenyl)pyrrole

1.67 g (5.3 mmol) of 1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole (prepared as described in Example 33) were dissolved in 30 ml of dimethylformamide, 0.50 ml (5.3 mmol) of phosphorous oxychloride was added to the resulting solution, and the mixture was then stirred at 60°C for 2 hours. At the end of this time, the reaction mixture was gradually added to ice-water and the pH of the mixture was adjusted to a value of 8 - 9 by the addition of sodium carbonate. The mixture was then extracted with ethyl acetate. The organic extract was washed with water and dried over anhydrous sodium sulfate, after which the solvent was removed by distillation under reduced pressure. The residue was applied to a silica gel chromatography column and eluted with a 5 : 1 by volume mixture of hexane and ethyl acetate, to give 0.90 g (yield 50%) of 1-(4-fluorophenyl)-5-formyl-2-(4-methylsulfonylphenyl)pyrrole as a white powder, melting at 135 - 137°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

9.55 (1H, singlet); 7.80 (2H, doublet, J = 9 Hz); 7.32 - 7.19 (5H, multiplet); 7.16 - 7.08 (2H, multiplet); 6.64 (1H, doublet, J = 4 Hz); 3.04 (3H, singlet).

2) 5-Difluoromethyl-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole

0.50 g (1.5 mmol) of 1-(4-fluorophenyl)-5-formyl-2-(4-methylsulfonylphenyl)pyrrole [prepared as described in step 1)] was dissolved in 3 ml of anhydrous diglyme, and 0.17 ml (2.9 mmol) of diethylaminosulfur trifluoride was added to the resulting solution. The mixture was then stirred at 100°C for 6 hours. At the end of this time, water was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was then removed by distillation under reduced pressure. The resulting residue was applied to a silica gel chromatography column and eluted with a 7 : 3 by volume mixture of hexane and ethyl acetate, to give 0.12 g (yield 23%) of 5-difluoromethyl-1-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)pyrrole as a slightly yellow powder, melting at 111 - 112°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.76 (2H, doublet, J = 9 Hz); 7.27 - 7.21 (5H, multiplet); 7.15 - 7.08 (2H, multiplet); 6.71 - 6.69 (1H, multiplet); 6.56 - 6.54 (1H, multiplet); 6.42 (1H, triplet, J = 54 Hz); 3.03 (3H, singlet).

Mass spectrum (EI) m/z: 365 [M⁺].

[EXAMPLE 49]

1-(4-Fluorophenyl)-4-difluoromethyl-2-(4-methylsulfonylphenyl)pyrrole

1) 1-(4-Fluorophenyl)-4-formyl-2-(4-methylsulfonylphenyl)pyrrole

0.58 g (1.7 mmol) of 1-(4-fluorophenyl)-4-hydroxymethyl-2-(4-methylsulfonylphenyl)pyrrole (prepared as described in Example 46) was dissolved in 30 ml of methylene chloride, and 2.40 g of manganese dioxide were added to the resulting solution. The mixture was then stirred at room temperature for 3 hours. At the end of this time, the reaction mixture was filtered using a Celite (trade mark) filter aid and the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was applied to a silica gel chromatography column and eluted with a 2 : 3 by volume mixture of ethyl acetate and hexane, to give 0.52 g (yield 90%) of 1-(4-fluorophenyl)-4-formyl-2-(4-methylsulfonylphenyl)pyrrole as a white powder, melting at 169 - 171 °C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

9.89 (1H, singlet); 7.82 (2H, doublet, J = 9 Hz); 7.56 (1H, doublet, J = 2 Hz); 7.29 (2H, doublet, J = 9 Hz); 7.22 - 7.08 (4H, multiplet); 6.99 (1H, doublet, J = 2 Hz); 3.06 (3H, singlet).

2) 1-(4-Fluorophenyl)-4-difluoromethyl-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 48, but using 1-(4-fluorophenyl)-4-formyl-2-(4-methylsulfonylphenyl)pyrrole [prepared as described in step 1)] and diethylaminosulfur trifluoride as starting materials, the title compound was obtained as a white powder (yield 16%), melting at 98 - 100 °C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.80 (2H, doublet, J = 9 Hz); 7.28 (2H, doublet, J = 9 Hz); 7.18 - 7.04 (5H, multiplet); 6.74 (1H, triplet, J = 57 Hz); 6.69 (1H, singlet); 3.05 (3H, singlet).

25 [EXAMPLE 50]

1-(4-Fluorophenyl)-4-difluoromethyl-5-methyl-2-(4-methylsulfonylphenyl)pyrrole

1) 1-(4-Fluorophenyl)-4-formyl-5-methyl-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 49-1), but using 1-(4-fluorophenyl)-4-hydroxymethyl-5-methyl-2-(4-methylsulfonylphenyl)pyrrole (prepared as described in Example 47) and manganese dioxide as starting materials, the title compound was obtained as a white powder (yield 98%), melting at 167 - 169 °C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

9.99 (1H, singlet); 7.75 (2H, doublet, $J = 9$ Hz); 7.24 - 7.16 (6H, multiplet); 6.94 (1H, singlet); 3.03 (3H, singlet); 2.42 (3H, singlet).

Mass spectrum (FAB) m/z : 358 $[(M+H)^+]$.

2) 1-(4-Fluorophenyl)-4-difluoromethyl-5-methyl-2-(4-methylsulfonylphenyl)pyrrole

5 Following a procedure similar to that described in Example 48, but using 1-(4-fluorophenyl)-4-formyl-5-methyl-2-(4-methylsulfonylphenyl)pyrrole [prepared as described in step 1)] and diethylaminosulfur trifluoride as starting materials, the title compound was obtained as a white powder (yield 70%), melting at 136 - 138°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, $CDCl_3$) δ ppm:

10 7.72 (2H, doublet, $J = 9$ Hz); 7.22 - 7.08 (6H, multiplet); 6.73 (1H, triplet, $J = 56$ Hz); 6.66 (1H, singlet); 3.02 (3H, singlet); 2.18 (3H, singlet).

Mass spectrum (EI) m/z : 379 $[M^+]$.

[EXAMPLE 51]

15 2-(4-Fluorophenyl)-4-phenyl-1-(4-sulfamoylphenyl)pyrrole

1) 3-(4-Fluorobenzoyl)-2-phenylpropionaldehyde

20 A 45% w/v solution of phenylacetaldehyde in diethyl phthalate containing 25.00 g (94 mmol) of phenylacetaldehyde was dissolved in 50 ml of toluene, and 7.96 g (94 mmol) of piperidine was added to the resulting solution. The mixture was then heated under reflux, while the water produced was removed, until the production of water stopped (about 1 hour). At the end of this time, the solvent was removed by distillation under reduced pressure, to give 31.78 g of a mixture of β -piperidinostyrene and diethyl phthalate as a red oily substance.

25 4.68 g of the β -piperidinostyrene/diethyl phthalate mixture were dissolved in 70 ml of anhydrous tetrahydrofuran, and 1.01 g (10 mmol) of triethylamine were added to the resulting solution. 2.60 g (12 mmol) of 4-fluorophenacyl bromide were then added to the resulting mixture, which was then stirred at room temperature for 3 hours. At the end of this time, 30 ml of 1 N aqueous hydrochloric acid were added to the reaction mixture, and the mixture was stirred at room temperature for a further 1 hour. It was then extracted with diethyl ether. The organic extract was washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure and the residue was applied to a silica gel chromatography column and eluted with a 95 : 5 by volume mixture of hexane

30

and ethyl acetate, to give 0.50 g of 3-(4-fluorobenzoyl)-2-phenylpropionaldehyde as a slightly yellow oily substance.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

9.80 (1H, singlet); 8.03 - 7.98 (2H, multiplet); 7.42 - 7.25 (5H, multiplet); 7.16 - 7.10 (2H, multiplet).

Mass spectrum (FAB) m/z: 257 [(M+H)⁺].

2) 2-(4-Fluorophenyl)-4-phenyl-1-(4-sulfamoylphenyl)pyrrole

0.32 g (1.25 mmol) of 3-(4-fluorobenzoyl)-2-phenylpropionaldehyde [prepared as described in step 1)] and 0.26 g (1.5 mmol) of 4-sulfamoylaniline were dissolved in 20 ml of acetic acid, and the mixture was heated under reflux for 4 hours. The solvent was then removed by distillation under reduced pressure and water was added to the residue, which was then extracted with ethyl acetate. The organic extract was washed with water and dried over anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure, and the residue was applied to a silica gel chromatography column and eluted with a 3 : 2 by volume mixture of hexane and ethyl acetate, to give 0.35 g (yield 60%) of 2-(4-fluorophenyl)-4-phenyl-1-(4-sulfamoylphenyl)pyrrole as a slightly yellow powder, melting at 192 - 194°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.91 (2H, doublet, J = 9 Hz); 7.58 (2H, doublet, J = 7 Hz); 7.39 - 7.22 (6H, multiplet); 7.18 - 7.12 (2H, multiplet); 6.99 (2H, triplet, J = 9 Hz); 6.73 (1H, doublet, J = 2 Hz); 4.84 (2H, singlet).

Mass spectrum (EI) m/z: 392 [M⁺].

[EXAMPLE 52]

2-(4-Methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

1) N-(4-Methoxybenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 4-methoxybenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a pale yellow powder (yield 95%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

8.35 (1H, singlet); 7.94 (2H, doublet, J = 9 Hz); 7.86 (2H, doublet, J = 9 Hz); 7.23 (2H, doublet, J = 9 Hz); 7.00 (2H, doublet, J = 9 Hz); 5.98 (2H, singlet); 3.90 (3H, singlet).

2) 4-Methoxy- α -(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-methoxybenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a pale yellow powder (yield 98%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.74 (2H, doublet, $J = 9$ Hz); 7.51 (2H, doublet, $J = 9$ Hz); 6.97 (2H, doublet, $J = 9$ Hz); 6.82 (2H, doublet, $J = 9$ Hz); 6.60 (1H, doublet, $J = 8$ Hz); 6.41 (2H, singlet); 5.54 (1H, doublet, $J = 8$ Hz); 3.84 (3H, singlet).

3) 2-(4-Methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 4-methoxy- α -(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and methacrolein as starting materials, the title compound was obtained as a pale brown powder (yield 6%), melting at 163 - 166°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.84 (2H, doublet, $J = 9$ Hz); 7.23 (2H, doublet, $J = 9$ Hz); 7.03 (2H, doublet, $J = 9$ Hz); 6.79 (2H, doublet, $J = 9$ Hz); 6.73 (1H, singlet); 6.23 (1H, singlet); 4.78 (2H, singlet); 3.79 (3H, singlet); 2.18 (3H, singlet).

Mass spectrum (EI) m/z : 342 [M^+].

[EXAMPLE 53]

1-(3,4-Dimethoxyphenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 3,4-dimethoxyaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a white powder, melting at 124 - 126°C. The yield of the compound (yellow powder) in the first stage was 96%, that in the second stage (brown prismatic crystals) was 48%, and that in the third stage was 15%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.75 (2H, doublet, $J = 7$ Hz); 7.30 (2H, doublet, $J = 7$ Hz); 6.98 (1H, multiplet); 6.84 (1H, doublet, $J = 8$ Hz); 6.74 - 6.70 (2H, multiplet); 6.57 (1H, multiplet); 6.39-6.37 (1H, multiplet); 3.92 (3H, singlet); 3.74 (3H, singlet); 3.03 (3H, singlet).

Mass spectrum (EI) m/z: 357 [M⁺].

[EXAMPLE 54]

1-(3-Fluoro-4-methoxyphenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using 3-fluoro-4-methoxyaniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as a pale yellow powder, melting at 116 - 118°C. The yield of the compound (pale yellow powder) in the first stage was 94%, that in the second stage (white powder) was 87%, and that in the third stage was 16%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.77 (2H, doublet, J = 9 Hz); 7.29 (2H, doublet, J = 9 Hz); 7.00 - 6.84 (4H, multiplet); 6.56 - 6.55 (1H, multiplet); 6.39 - 6.37 (1H, multiplet); 3.92 (3H, singlet); 3.05 (3H, singlet).

Mass spectrum (EI) m/z: 345 [M⁺].

[EXAMPLE 55]

1-Phenyl-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in the three stages of Examples 1-1), -2) and -3), but using aniline as a starting material instead of 4-methoxyaniline, the title compound was obtained as white prismatic crystals, melting at 140 - 142°C. The yield of the compound (pale yellow powder) in the first stage was 76%, that in the second stage (pale yellow powder) was 95%, and that in the third stage was 16%.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.74 (2H, doublet, J = 8 Hz); 7.40 - 7.33 (3H, multiplet); 7.27 (2H, doublet, J = 8 Hz); 7.18 - 7.15 (2H, multiplet); 7.00 (1H, multiplet); 6.59 - 6.58 (1H, multiplet); 6.41 - 6.39 (1H, multiplet); 3.03 (3H, singlet).

[EXAMPLE 56]

4-Methyl-1-(3,4-dimethylphenyl)-2-(4-methylsulfonylphenyl)pyrrole

Following a procedure similar to that described in Example 8, but using methacrolein instead of acrolein in the third stage, the title compound was obtained as a pale yellow powder (yield 58%), melting at 126 - 128°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.72 (2H, doublet, J = 9 Hz); 7.27 - 7.24 (2H, multiplet); 7.08 - 7.05 (1H, multiplet); 6.96 (1H, singlet); 6.83 - 6.79 (1H, multiplet); 6.74 (1H, singlet); 6.41 (1H, singlet); 3.03 (3H, singlet); 2.27 (3H, singlet); 2.23 (3H, singlet); 2.18 (3H, singlet).

Mass spectrum (EI) m/z: 339 [M⁺].

5

[EXAMPLE 57]

1-(4-Methylphenyl)-2-(4-sulfamoylphenyl)pyrrole

1) N-(4-Sulfamoylbenzylidene)-4-methylaniline

Following a procedure similar to that described in Example 1-1), but using 4-sulfamoylbenzaldehyde and 4-methylaniline as starting materials, the title compound was obtained as a yellow powder (yield 82%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.56 (1H, singlet); 8.01 (4H, singlet); 7.27 - 7.12 (6H, multiplet); 2.38 (3H, singlet).

15 2) α -(4-Methylanilino)-4-sulfamoylphenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-sulfamoylbenzylidene)-4-methylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a pale yellow powder (yield 60%).

20 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.99 (2H, doublet, J = 8 Hz); 7.75 (2H, doublet, J = 8 Hz); 7.03 (2H, doublet, J = 8 Hz); 6.89 (2H, singlet); 6.69 (2H, doublet, J = 8 Hz); 5.70 - 5.55 (2H, multiplet); 2.25 (3H, singlet).

3) 1-(4-Methylphenyl)-2-(4-sulfamoylphenyl)pyrrole

25 Following a procedure similar to that described in Example 1-3), but using α -(4-methylanilino)-4-sulfamoylphenylacetonitrile [prepared as described in step 2)] and acrolein as starting materials, the title compound was obtained as a pale brown powder (yield 28%), melting at 131 - 134°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

30 7.73 (2H, doublet, J = 8 Hz); 7.24 (2H, doublet, J = 8 Hz); 7.16 (2H, doublet, J = 8 Hz); 7.04 (2H, doublet, J = 8 Hz); 6.96 (1H, triplet, J = 2 Hz); 6.55 (1H, doublet of doublets, J = 3 & 2 Hz); 6.38 (1H, triplet, J = 3 Hz); 4.74 (2H, singlet); 2.38 (3H, singlet).

Mass spectrum (EI) m/z: 312 [M⁺].

[EXAMPLE 58]

4-Methyl-1-(4-methylphenyl)-2-(4-sulfamoylphenyl)pyrrole

5 Following a procedure similar to that described in Example 57-3), but using methacrolein instead of acrolein, the title compound was obtained as a yellow powder (yield 42%), melting at 144 - 147°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.71 (2H, doublet, J = 8 Hz); 7.21 (2H, doublet, J = 8 Hz); 7.14 (2H, doublet, J = 8 Hz); 7.01
10 (2H, doublet, J = 8 Hz); 6.74 (1H, singlet); 6.39 (1H, singlet); 4.71 (2H, singlet); 2.37 (3H, singlet); 2.18 (3H, singlet).

Mass spectrum (EI) m/z: 326 [M⁺].

[EXAMPLE 59]

15 1-(4-Chlorophenyl)-2-(4-sulfamoylphenyl)pyrrole

1) N-(4-Sulfamoylbenzylidene)-4-chloroaniline

Following a procedure similar to that described in Example 1-1), but using 4-sulfamoylbenzaldehyde and 4-chloroaniline as starting materials, the title compound was obtained as a pale yellow powder (yield 72%).

20 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

8.52 (1H, singlet); 8.02 (4H, singlet); 7.38 (2H, doublet, J = 9 Hz); 7.20 (2H, doublet, J = 9 Hz); 6.87 (2H, singlet).

2) α-(4-Chloroanilino)-4-sulfamoylphenylacetonitrile

25 Following a procedure similar to that described in Example 1-2), but using N-(4-Sulfamoylbenzylidene)-4-chloroaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a white powder (yield 93%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

30 7.99 (2H, doublet, J = 8 Hz); 7.74 (2H, doublet, J = 8 Hz); 7.14 (2H, doublet, J = 9 Hz); 7.12 (2H, singlet); 6.74 (2H, doublet, J = 9 Hz); 6.52 (1H, doublet, J = 9 Hz); 5.69 (1H, doublet, J = 9 Hz).

3) 1-(4-Chlorophenyl)-2-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using α -(4-chloroanilino)-4-sulfamoylphenylacetonitrile [prepared as described in step 2)] and acrolein as starting materials, the title compound was obtained as a pale yellow powder (yield 38%), melting at 179 - 181°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.77 (2H, doublet, J = 9 Hz); 7.34 (2H, doublet, J = 9 Hz); 7.23 (2H, doublet, J = 9 Hz); 7.10 (2H, doublet, J = 9 Hz); 6.96 (1H, triplet, J = 2 Hz); 6.56 (1H, doublet of doublets, J = 3 & 2 Hz); 6.40 (1H, triplet, J = 3 Hz); 4.78 (2H, singlet).

Mass spectrum (EI) m/z: 332 [M⁺].

[EXAMPLE 60]

1-(4-Chlorophenyl)-4-methyl-2-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 59-3), but using methacrolein instead of acrolein, the title compound was obtained as a pale yellow powder (yield 53%), melting at 171 - 173°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.75 (2H, doublet, J = 8 Hz); 7.31 (2H, doublet, J = 8 Hz); 7.21 (2H, doublet, J = 8 Hz); 7.06 (2H, doublet, J = 8 Hz); 6.74 (1H, singlet); 6.41 (1H, singlet); 4.80 (2H, singlet); 2.18 (3H, singlet).

Mass spectrum (EI) m/z: 346 [M⁺].

[EXAMPLE 61]

1-(4-Methoxyphenyl)-2-(4-sulfamoylphenyl)pyrrole

1) N-(4-Sulfamoylbenzylidene)-4-methoxyaniline

Following a procedure similar to that described in Example 1-1), but using 4-sulfamoylbenzaldehyde and 4-methoxyaniline as starting materials, the title compound was obtained as a pale yellow powder (yield 85%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.74 (1H, singlet); 8.09 (2H, doublet, J = 8 Hz); 7.95 (2H, doublet, J = 8 Hz); 7.48 (2H, singlet); 7.37 (2H, doublet, J = 9 Hz); 7.01 (2H, doublet, J = 9 Hz); 3.80 (3H, singlet).

2) α -(4-Methoxyanilino)-4-sulfamoylphenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-sulfamoylbenzylidene)-4-methoxyaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a white powder (yield 68%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.91 (2H, doublet, J = 8 Hz); 7.76 (2H, doublet, J = 8 Hz); 7.43 (2H, singlet); 6.80 (4H, multiplet); 6.40 (1H, doublet, J = 10 Hz); 6.03 (1H, doublet, J = 10 Hz); 3.67 (3H, singlet).

3) 1-(4-Methoxyphenyl)-2-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using α -(4-methoxyanilino)-4-sulfamoylphenylacetonitrile [prepared as described in step 2)] and acrolein as starting materials, the title compound was obtained as a yellow powder (yield 9%), melting at 112 - 114°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.78 - 7.68 (2H, multiplet); 7.26 - 6.85 (7H, multiplet); 6.53 - 6.51 (1H, multiplet); 6.37 - 6.35 (1H, multiplet); 5.07 (2H, singlet); 3.81 (3H, singlet).

Mass spectrum (EI) m/z: 328 [M⁺].

[EXAMPLE 62]

1-(4-Methoxyphenyl)-4-methyl-2-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 61-3), but using methacrolein instead of acrolein, the title compound was obtained as a pale yellow powder (yield 35%), melting at 63 - 64°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.69 (2H, doublet, J = 8 Hz); 7.18 (2H, doublet, J = 8 Hz); 7.05 (2H, doublet, J = 9 Hz); 6.85 (2H, doublet, J = 9 Hz); 6.72 (1H, singlet); 6.38 (1H, singlet); 5.04 (2H, singlet); 3.80 (3H, singlet); 2.18 (3H, singlet).

Mass spectrum (EI) m/z: 342 [M⁺].

[EXAMPLE 63]

4-Butyl-1-(4-methoxyphenyl)-2-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 61-3), but using 2-butyraldehyde instead of acrolein, the title compound was obtained as a pale yellow powder (yield 85%), melting at 115 - 117°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

5 7.70 (2H, doublet, J = 8 Hz); 7.26 - 7.19 (2H, multiplet); 7.08 - 7.05 (2H, multiplet); 6.88 - 6.87 (2H, multiplet); 6.72 (1H, singlet); 6.41 - 6.40 (1H, multiplet); 4.89 (2H, singlet); 3.82 (3H, singlet); 2.53 (2H, triplet, J = 8 Hz); 1.68 - 1.57 (2H, multiplet); 1.49 - 1.36 (2H, multiplet); 0.95 (3H, triplet, J = 7 Hz).

Mass spectrum (EI) m/z: 384 [M⁺].

10

[EXAMPLE 64]

4-Ethyl-2-(4-methoxyphenyl)-1-(4-sulfamoylphenyl)pyrrole

1) 1-(N,N-Diisopropylamino)-1-butene

6.25 ml (69.3 mmol) of butyraldehyde and 19.44 ml (139 mmol) of diisopropylamine
15 were dissolved in 30 ml of benzene, and the mixture was heated under reflux, while removing the water produced, until the production of water stopped (about 15 hours). The solvent was then removed by distillation under reduced pressure, and the residue was distilled under atmospheric pressure. Those fractions of the distillate having a boiling point of from 140 to 160°C were collected, to give 6.95 g of the title compound as a pale yellow oily substance
20 (yield 65%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

5.94 (1H, doublet, J = 14 Hz); 4.05 (1H, doublet of triplets, J = 14 & 7 Hz); 3.50 - 3.34 (2H, multiplet); 2.01 - 1.88 (2H, multiplet); 1.03 (6H, doublet, J = 7 Hz); 0.91 (3H, triplet, J = 7 Hz).

25 2) 2-(4-Methoxyphenacyl)butyraldehyde

1.00 g (6.4 mmol) of 1-(N,N-diisopropylamino)-1-butene [prepared as described in step 1)] was dissolved in 10 ml of benzene, and 0.98 g (4.3 mmol) of 4-methoxyphenacyl bromide was added dropwise to the resulting solution with stirring, whilst ice-cooling. The reaction mixture was stirred, whilst ice-cooling, for 15 minutes, and then at room temperature for 48
30 hours. At the end of this time, 9 ml of 1 N aqueous hydrochloric acid was added to the mixture, and the mixture was stirred for 15 minutes. It was then neutralised, by the addition of concentrated aqueous ammonia, and extracted with ethyl acetate. The organic extract was

washed with water and dried over anhydrous magnesium sulfate, after which the solvent was removed by distillation under reduced pressure. The residue was applied to a silica gel chromatography column and eluted with a 4 : 1 by volume mixture of hexane and ethyl acetate, to give 0.47 g (yield 49%) of the title compound as a pale yellow oily substance.

5 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

9.83 (1H, singlet); 7.96 (2H, doublet, $J = 9$ Hz); 6.94 (2H, doublet, $J = 9$ Hz); 3.88 (3H, singlet); 3.49 - 3.33 (1H, multiplet); 3.09 - 2.93 (1H, multiplet); 1.92 - 1.74 (1H, multiplet); 1.70 - 1.54 (1H, multiplet); 1.01 (3H, triplet, $J = 7$ Hz).

3) 4-Ethyl-2-(4-methoxyphenyl)-1-(4-sulfamoylphenyl)pyrrole

10 0.47 g (2.1 mmol) of 2-(4-methoxyphenacyl)butyraldehyde [prepared as described in step 2)] and 0.44 g (2.5 mmol) of 4-sulfamoylaniline were dissolved in 5 ml of acetic acid, and the resulting solution was heated under reflux for 2 hours. At the end of this time, the mixture was cooled to room temperature, concentrated aqueous ammonia was added to adjust its pH to a value of 8.0 and the mixture was extracted with ethyl acetate. The organic extract
15 was washed with water, dried over anhydrous magnesium sulfate and then concentrated by evaporation under reduced pressure. The residue was applied to a silica gel chromatography column, eluted with a 3 : 2 by volume mixture of hexane and ethyl acetate, to give 0.57 g (yield 76%) of the title compound as a pale yellow powder, melting at 154 - 156°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

20 7.84 (2H, doublet, $J = 9$ Hz); 7.24 (2H, doublet, $J = 9$ Hz); 7.04 (2H, doublet, $J = 9$ Hz); 6.79 (2H, doublet, $J = 9$ Hz); 6.74 (1H, singlet); 6.27 (1H, singlet); 4.78 (2H, singlet); 3.79 (3H, singlet); 2.57 (2H, quartet, $J = 8$ Hz); 1.26 (3H, triplet, $J = 8$ Hz).

[EXAMPLE 65]

25 2-(4-Chlorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

1) 1-(N,N-Diisobutylamino)-1-propene

Following a procedure similar to that described in Example 64-1), but using propionaldehyde and diisobutylamine as starting materials, the title compound was obtained as a colorless oily substance (yield 29%), boiling at 63 - 66°C/10mmHg

30 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

5.89 (1H, doublet, $J = 14$ Hz); 3.92 - 3.79 (1H, multiplet); 2.66 (2H, doublet, $J = 7$ Hz); 1.92 - 1.74 (2H, multiplet); 1.54 (3H, doublet, $J = 7$ Hz); 0.80 (12H, doublet, $J = 7$ Hz).

2) 2-(4-Chlorophenacyl)propionaldehyde

Following a procedure similar to that described in Example 64-2), but using 1-(N,N-diisobutylamino)-1-propene [prepared as described in step 1)] and 4-chlorophenacyl bromide as starting materials, the title compound was obtained as a pale brown oily substance (yield 39%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

9.79 (1H, singlet); 7.92 (2H, doublet, J = 9 Hz); 7.45 (2H, doublet, J = 9 Hz); 3.47 (1H, doublet of doublets, J = 18 & 7 Hz); 3.22 - 3.04 (1H, multiplet); 2.95 (1H, doublet of doublets, J = 18 & 7 Hz); 1.25 (3H, doublet, J = 7 Hz).

3) 2-(4-Chlorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 64-3), but using 2-(4-chlorophenacyl)propionaldehyde [prepared as described in step 2)] and 4-sulfamoylaniline as starting materials, the title compound was obtained as a pale brown powder (yield 35%), melting at 196 - 198°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.85 (2H, doublet, J = 9 Hz); 7.36 (2H, doublet, J = 9 Hz); 7.22 (2H, doublet, J = 9 Hz); 7.03 (2H, doublet, J = 9 Hz); 6.75 (1H, singlet); 6.30 (1H, singlet); 4.80 (2H, singlet); 2.17 (3H, singlet).

Mass spectrum (EI) m/z: 342 [M⁺].

[EXAMPLE 66]

4-Methyl-2-(4-methylthiophenyl)-1-(4-sulfamoylphenyl)pyrrole

1) N-(4-Methylthiobenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 4-methylthiobenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a yellow powder (yield 88%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.46 (1H, singlet); 7.90 (2H, doublet, J = 9 Hz); 7.84 (2H, doublet, J = 8 Hz); 7.33 (2H, doublet, J = 9 Hz); 7.27 (2H, doublet, J = 8 Hz); 7.15 (2H, broad singlet); 2.55 (3H, singlet).

2) 4-Methylthio- α -(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-methylthiobenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a yellow powder (yield 100%).

- 5 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.66 (2H, doublet, $J = 9$ Hz); 7.52 (2H, doublet, $J = 8$ Hz); 7.31 (2H, doublet, $J = 8$ Hz); 7.25 - 7.13 (1H, multiplet); 6.90 (2H, broad singlet); 6.86 (2H, doublet, $J = 9$ Hz); 5.89 - 5.83 (1H, multiplet); 2.50 (3H, singlet).

- 10 3) 4-Methyl-2-(4-methylthiophenyl)-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 4-methylthio- α -(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and methacrolein as starting materials, the title compound was obtained as pale brown scaly crystals (yield 31%), melting at 172 - 173°C.

- 15 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.85 (2H, doublet, $J = 9$ Hz); 7.24 (2H, doublet, $J = 9$ Hz); 7.12 (2H, doublet, $J = 9$ Hz); 7.02 (2H, doublet, $J = 8$ Hz); 6.74 (1H, doublet, $J = 2$ Hz); 6.29 (1H, doublet, $J = 2$ Hz); 4.82 (2H, broad singlet); 2.47 (3H, singlet).

Mass spectrum (EI) m/z : 358 [M^+].

20

[EXAMPLE 67]

2-(4-Ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

- 1) N-(4-Ethoxybenzylidene)-4-sulfamoylaniline

- 25 Following a procedure similar to that described in Example 1-1), but using 4-ethoxybenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a pale yellow powder (yield 76%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

- 30 8.38 (1H, singlet); 7.88 (2H, doublet, $J = 9$ Hz); 7.85 (2H, doublet, $J = 9$ Hz); 7.24 (2H, doublet, $J = 9$ Hz); 6.98 (2H, doublet, $J = 9$ Hz); 4.12 (2H, quartet, $J = 7$ Hz); 1.45 (3H, triplet, $J = 7$ Hz).

- 2) 4-Ethoxy- α -(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-ethoxybenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a slightly yellow powder (yield 88%).

5 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.65 (2H, doublet, $J = 8$ Hz); 7.48 (2H, doublet, $J = 8$ Hz); 7.20 - 7.03 (1H, multiplet); 6.99 - 6.80 (6H, multiplet); 5.88 - 5.76 (1H, multiplet); 4.04 (2H, quartet, $J = 7$ Hz); 1.38 (3H, triplet, $J = 7$ Hz).

10 3) 2-(4-Ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 4-ethoxy- α -(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and methacrolein as starting materials, the title compound was obtained as a brown powder (yield 3%), melting at 135 - 139°C.

15 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.83 (2H, doublet, $J = 9$ Hz); 7.22 (2H, doublet, $J = 9$ Hz); 7.02 (2H, doublet, $J = 9$ Hz); 6.77 (2H, doublet, $J = 9$ Hz); 6.72 (1H, broad singlet); 6.23 (1H, doublet, $J = 2$ Hz); 4.79 (2H, broad singlet); 4.03 (2H, quartet, $J = 7$ Hz); 2.17 (3H, singlet); 1.41 (3H, triplet, $J = 7$ Hz).
Mass spectrum (EI) m/z : 356 [M^+].

20

[EXAMPLE 68]

4-Methyl-2-(4-propoxyphenyl)-1-(4-sulfamoylphenyl)pyrrole

1) N-(4-Propoxybenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 4-

25 propoxybenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a pale yellow powder (yield 84%)

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.38 (1H, singlet); 7.92 (2H, doublet, $J = 9$ Hz); 7.85 (2H, doublet, $J = 9$ Hz); 7.23 (2H, doublet, $J = 8$ Hz); 6.99 (2H, doublet, $J = 8$ Hz); 6.81 (2H, broad singlet); 4.01 (2H, triplet, $J = 6$ Hz); 1.91 - 1.78 (2H, multiplet); 1.07 (3H, triplet, $J = 7$ Hz).

30 2) 4-Propoxy- α -(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-propoxybenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a pale yellow powder (yield 80%).

5 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.68 (2H, doublet, $J = 9$ Hz); 7.51 (2H, doublet, $J = 8$ Hz); 7.20 - 7.14 (1H, broad doublet, $J = 8$ Hz); 6.98 (2H, doublet, $J = 9$ Hz); 6.92 (2H, broad singlet); 6.88 (2H, doublet, $J = 9$ Hz); 5.83 - 5.80 (1H, broad doublet, $J = 8$ Hz); 3.96 (2H, triplet, $J = 6$ Hz); 1.87 - 1.74
10 (2H, multiplet); 1.04 (3H, triplet, $J = 7$ Hz).

3) 4-Methyl-2-(4-propoxyphenyl)-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 4-propoxy- α -(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and methacrolein as starting materials, the title compound was obtained as a pale brown powder (yield 5%),
15 melting at 142 - 145°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.83 (2H, doublet, $J = 9$ Hz); 7.23 (2H, doublet, $J = 9$ Hz); 7.02 (2H, doublet, $J = 9$ Hz); 6.78 (2H, doublet, $J = 9$ Hz); 6.72 (1H, doublet, $J = 2$ Hz); 6.23 (1H, doublet, $J = 2$ Hz); 5.86 (2H, broad singlet); 3.90 (2H, triplet, $J = 7$ Hz); 1.89 - 1.84 (2H, multiplet); 1.03 (3H, triplet, $J = 7$ Hz).
20

Mass spectrum (EI) m/z : 370 [M^+].

[EXAMPLE 69]

4-Methyl-2-(4-methoxy-3-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole

25 1) N-(4-Methoxy-3-methylbenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 4-methoxy-3-methylbenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a yellow powder (yield 92%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

30 8.85 & 8.31 (total: 1H, each singlet); 7.93 (1H, doublet, $J = 8$ Hz); 7.77 - 7.65 (2H, multiplet); 7.26 - 7.23 (2H, multiplet); 6.91 - 6.86 (1H, multiplet); 6.71 - 6.88 (1H, multiplet); 4.77 & 4.14 (total: 1H, each singlet); 3.92 (3H, singlet); 2.28 & 2.21 (total: 3H, each singlet).

2) 4-Methoxy-3-methyl- α -(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(4-methoxy-3-methylbenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a white powder (yield 63%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.62 (2H, doublet, $J = 8$ Hz); 7.39 - 7.34 (2H, multiplet); 7.26 (1H, doublet, $J = 9$ Hz); 7.04 - 7.02 (3H, multiplet); 6.90 (2H, doublet, $J = 8$ Hz); 5.97 (1H, doublet, $J = 9$ Hz); 3.81 (3H, singlet); 3.33 (3H, singlet).

3) 4-Methyl-2-(4-methoxy-3-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 4-methoxy-3-methyl- α -(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and methacrolein as starting materials, the title compound was obtained as a pale yellow powder (yield 39%), melting at 149 - 151°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.82 (2H, doublet, $J = 9$ Hz); 7.26 - 7.20 (2H, multiplet); 6.99 (1H, singlet); 6.81 - 6.65 (3H, multiplet); 6.22 (1H, singlet); 4.90 (2H, singlet); 3.79 (3H, singlet); 2.17 (3H, singlet); 2.14 (3H, singlet).

Mass spectrum (EI) m/z : 332 [M^+].

[EXAMPLE 70]

2-(3,4-Dichlorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

1) N-(3,4-Dichlorobenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 3,4-dichlorobenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a white powder (yield 52%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.49 (1H, singlet); 8.09 (1H, doublet, $J = 2$ Hz); 7.94 (1H, doublet, $J = 9$ Hz); 7.82 (1H, doublet of doublets, $J = 2$ & 8 Hz); 7.63 (1H, doublet, $J = 8$ Hz); 7.30 (2H, doublet, $J = 9$ Hz); 7.10 (2H, broad singlet).

2) 3,4-Dichloro- α -(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(3,4-dichlorobenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a white powder (yield 91%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.76 (1H, doublet, $J = 2$ Hz); 7.70 (2H, doublet, $J = 9$ Hz); 7.60 (1H, doublet, $J = 8$ Hz); 7.53 (1H, doublet of doublets, $J = 2$ & 8 Hz); 7.24 (1H, broad doublet, $J = 9$ Hz); 6.84 (2H, broad singlet); 6.83 (2H, doublet, $J = 9$ Hz); 5.92 (1H, broad doublet, $J = 9$ Hz).

3) 2-(3,4-Dichlorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 3,4-dichloro- α -(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and methacrolein as starting materials, the title compound was obtained as a pale brown powder (yield 33%), melting at 136 - 138°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.89 (2H, doublet, $J = 9$ Hz); 7.30 (1H, doublet, $J = 3$ Hz); 7.29 (1H, doublet, $J = 9$ Hz); 7.24 (2H, doublet, $J = 9$ Hz); 6.79 (1H, doublet of doublets, $J = 2$ & 9 Hz); 6.76 (1H, doublet, $J = 2$ Hz); 6.34 (1H, doublet, $J = 2$ Hz); 4.83 (2H, broad singlet); 2.17 (3H, singlet).

Mass spectrum (EI) m/z : 380 [M^+].

[EXAMPLE 71]

2-(3-Fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

1) N-(3-Fluoro-4-methoxybenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 3-fluoro-4-methoxybenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a slightly yellow powder (yield 57%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.40 (1H, singlet); 7.92 (2H, doublet, $J = 9$ Hz); 7.74 (1H, doublet of doublets, $J = 2$ & 9 Hz); 7.62 (1H, doublet, $J = 9$ Hz); 7.25 (2H, doublet, $J = 9$ Hz); 7.12 (1H, triplet, $J = 8$ Hz); 7.02 (2H, broad singlet); 3.97 (3H, singlet).

2) 3-Fluoro-4-methoxy- α -(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(3-fluoro-4-methoxybenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a slightly yellow powder (yield 98%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.69 (2H, doublet, $J = 9$ Hz); 7.37 - 7.33 (2H, multiplet); 7.13 - 7.05 (1H, broad singlet); 7.12 (1H, triplet, $J = 9$ Hz); 6.83 (2H, doublet, $J = 9$ Hz); 6.79 (2H, broad singlet); 5.77 - 5.73 (1H, multiplet); 3.91 (3H, singlet).

3) 2-(3-Fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 3-fluoro-4-methoxy- α -(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and methacrolein as starting materials, the title compound was obtained as a white powder (yield 28%), melting at 170 - 173°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.86 (2H, doublet, $J = 9$ Hz); 7.23 (2H, doublet, $J = 9$ Hz); 6.90 - 6.81 (3H, multiplet); 6.79 (1H, doublet, $J = 2$ Hz); 6.74 (1H, doublet, $J = 2$ Hz); 4.82 (2H, broad singlet); 3.87 (3H, singlet); 2.17 (3H, singlet).

Mass spectrum (EI) m/z : 360 [M^+].

[EXAMPLE 72]

2-(2,4-Difluorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

1) N-(2,4-Difluorobenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 2,4-difluorobenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a pale yellow powder (yield 52%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

8.67 (1H, singlet); 8.20 (1H, doublet of triplets, $J = 7$ & 9 Hz); 7.97 (2H, doublet of doublets, $J = 2$ & 7 Hz); 7.28 (2H, doublet of doublets, $J = 2$ & 7 Hz); 7.05 - 6.98 (1H, multiplet); 6.95 - 6.87 (1H, multiplet); 4.88 (2H, broad singlet).

2) 2,4-Difluoro- α -(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(2,4-difluorobenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a pale yellow powder (yield 88%).

5 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.76 (2H, doublet, $J = 9$ Hz); 7.71 - 7.65 (1H, multiplet); 7.05 - 6.92 (2H, multiplet); 6.82 (2H, doublet, $J = 9$ Hz); 6.79 (1H, multiplet); 6.37 (2H, broad singlet); 5.73 (1H, doublet, $J = 9$ Hz).

10 3) 2-(2,4-Difluorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 2,4-difluoro- α -(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and methacrolein as starting materials, the title compound was obtained as a pale brown powder (yield 32%), melting at 170 - 172°C.

15 Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.84 (2H, doublet, $J = 9$ Hz); 7.20 (2H, doublet, $J = 9$ Hz); 7.21 - 7.13 (1H, multiplet); 6.87 - 6.67 (2H, multiplet); 6.80 (1H, broad singlet); 6.31 (1H, broad singlet); 4.85 (2H, broad singlet); 2.19 (3H, singlet).

Mass spectrum (EI) m/z : 348 [M^+].

20

[EXAMPLE 73]

2-(4-Methoxyphenyl)-3-methyl-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 52-3), but using crotonaldehyde instead of methacrolein, the title compound was obtained as a brown amorphous powder (yield 21%).

25

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.79 (2H, doublet, $J = 9$ Hz); 7.16 (2H, doublet, $J = 9$ Hz); 7.01 (2H, doublet, $J = 9$ Hz); 6.88 (1H, doublet, $J = 3$ Hz); 6.83 (2H, doublet, $J = 9$ Hz); 6.28 (1H, doublet, $J = 3$ Hz); 4.86 (2H, singlet); 3.80 (3H, singlet); 2.14 (3H, singlet).

30 Mass spectrum (EI) m/z : 342 [M^+].

[EXAMPLE 74]

2-(3,4-Difluorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

1) N-(3,4-Difluorobenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 3,4-difluorobenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a slightly yellow powder (yield 67%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.40 (1H, singlet); 7.96 (2H, doublet of doublets, $J = 7$ & 2 Hz); 7.89 - 7.81 (1H, multiplet); 7.67 - 7.62 (1H, multiplet); 7.37 - 7.24 (1H, multiplet); 7.25 (2H, doublet of doublets, $J = 7$ & 2 Hz); 6.71 (2H, broad singlet).

2) 3,4-Difluoro- α -(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(3,4-difluorobenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a slightly yellow powder (yield 92%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.76 (2H, doublet, $J = 9$ Hz); 7.52 - 7.24 (3H, multiplet); 6.82 - 6.79 (3H, multiplet); 6.28 (2H, broad singlet); 5.64 (1H, doublet, $J = 8$ Hz).

3) 2-(3,4-Difluorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 3,4-difluoro- α -(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and methacrolein as starting materials, the title compound was obtained as a pale yellow powder (yield 51%), melting at 177 - 179°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

7.88 (2H, doublet of doublets, $J = 2$ & 7 Hz); 7.23 (2H, doublet of doublets, $J = 2$ & 7 Hz); 7.08 - 6.89 (2H, multiplet); 6.81 - 6.76 (1H, multiplet); 6.74 (1H, doublet, $J = 2$ Hz); 6.29 (1H, doublet, $J = 2$ Hz); 4.99 (2H, broad singlet); 2.17 (3H, singlet).

Mass spectrum (EI) m/z : 348 [M^+].

[EXAMPLE 75]

1-(2,4-Difluorophenyl)-4-methyl-2-(4-sulfamoylphenyl)pyrrole

1) 2,4-Difluoro-N-(4-sulfamoylbenzylidene)aniline

Following a procedure similar to that described in Example 1-1), but using 4-sulfamoylbenzaldehyde and 2,4-difluoroaniline as starting materials, the title compound was obtained as a white powder (yield 47%).

5 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.79 (1H, singlet); 8.12 (2H, doublet, $J = 8$ Hz); 7.97 (2H, doublet, $J = 8$ Hz); 7.58 - 7.34 (4H, multiplet); 7.21 - 7.13 (1H, multiplet).

2) α -(2,4-Difluoroanilino)-4-sulfamoylphenylacetonitrile

10 Following a procedure similar to that described in Example 1-2), but using 2,4-difluoro-N-(4-sulfamoylbenzylidene)aniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a white powder (yield 100%).

15 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.91 (2H, doublet, $J = 8$ Hz); 7.76 (2H, doublet, $J = 8$ Hz); 7.44 (2H, singlet); 7.25 - 7.17 (1H, multiplet); 6.97 - 6.94 (2H, multiplet); 6.73 (1H, doublet, $J = 10$ Hz); 6.17 (1H, doublet, $J = 10$ Hz).

3) 1-(2,4-Difluorophenyl)-4-methyl-2-(4-sulfamoylphenyl)pyrrole

20 Following a procedure similar to that described in Example 1-3), but using α -(2,4-difluoroanilino)-4-sulfamoylphenylacetonitrile [prepared as described in step 2)] and methacrolein as starting materials, the title compound was obtained as a white powder (yield 63%), melting at 140 - 141°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl_3) δ ppm:

25 7.75 (2H, doublet, $J = 8$ Hz); 7.23 - 7.16 (3H, multiplet); 6.94 - 6.88 (2H, multiplet); 6.69 (1H, singlet); 6.43 (1H, singlet); 4.99 (2H, singlet); 2.20 (3H, singlet).

Mass spectrum (EI) m/z : 348 [M^+].

[EXAMPLE 76]

30 2-(4-Methoxyphenyl)-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 52-3), but using acrolein instead of methacrolein, the title compound was obtained as a pale brown powder (yield 10%), melting at 183 - 184°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.92 - 7.84 (2H, multiplet); 7.39 - 7.23 (2H, multiplet); 7.11 - 7.04 (2H, multiplet); 6.95 - 6.93 (1H, multiplet); 6.82 - 6.78 (2H, multiplet); 6.39 (2H, multiplet); 4.84 (2H, singlet); 3.80 (3H, singlet).

Mass spectrum (EI) m/z: 342 [M⁺].

[EXAMPLE 77]

4-Methyl-2-phenyl-1-(4-sulfamoylphenyl)pyrrole

1) N-Benzylidene-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using benzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a pale yellow powder (yield 91%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.45 (1H, singlet); 7.97 - 7.90 (2H, multiplet); 7.95 (2H, doublet, J = 9 Hz); 7.57 - 7.47 (3H, multiplet); 7.25 (2H, doublet, J = 9 Hz); 6.74 (2H, broad singlet).

2) α-(4-Sulfamoylanilino)phenyl acetonitrile

Following a procedure similar to that described in Example 1-2), but using N-benzylidene-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a slightly yellow powder (yield 96%).

Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.78 (2H, doublet, J = 9 Hz); 7.64 - 7.61 (2H, multiplet); 7.55 - 7.47 (3H, multiplet); 6.85 (2H, doublet, J = 9 Hz); 6.52 (1H, broad doublet, J = 8 Hz); 6.24 (2H, broad singlet); 5.66 (1H, broad doublet, J = 8 Hz).

3) 4-Methyl-2-phenyl-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using α-(4-sulfamoylanilino)phenyl acetonitrile [prepared as described in step 2)] and methacrolein as

starting materials, the title compound was obtained as a pale yellow powder (yield 47%), melting at 165 - 168°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

- 7.84 (2H, doublet of doublets, J = 2 & 7 Hz); 7.23 (2H, doublet of doublets, J = 2 & 7 Hz);
5 7.28 - 7.20 (3H, multiplet); 7.12 - 7.09 (2H, multiplet); 6.75 (1H, doublet, J = 2 Hz); 6.31
(1H, doublet, J = 2 Hz); 4.88 (2H, broad singlet); 2.18 (3H, singlet).
Mass spectrum (EI) m/z: 312 [M⁺].

[EXAMPLE 78]

10 4-Methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl)pyrrole

1) N-(3,4-Dimethylbenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 3,4-dimethylbenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a pale yellow powder (yield 45%).

15 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.36 (1H, singlet); 7.92 (2H, doublet, J = 9 Hz); 7.69 (1H, doublet, J = 2 Hz); 7.59 (1H, doublet of doublets, J = 1 & 7 Hz); 7.26 - 7.08 (1H, multiplet); 7.22 (2H, doublet, J = 9 Hz); 6.46 (2H, broad singlet); 2.34 (6H, singlet).

20 2) 3,4-Dimethyl-α-(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-3,4-dimethylbenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a slightly yellow powder (yield 91%).

25 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.72 (2H, doublet, J = 9 Hz); 7.34 (1H, singlet); 7.30 (1H, doublet, J = 8 Hz); 7.20 (1H, doublet, J = 8 Hz); 6.82 (2H, doublet, J = 9 Hz); 6.74 - 6.70 (1H, broad multiplet); 6.56 (2H, broad multiplet); 5.54 (1H, broad doublet, J = 8 Hz); 2.30 (3H, singlet); 2.29 (3H, singlet).

30 3) 4-Methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 3,4-dimethyl-α-(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and

methacrolein as starting materials, the title compound was obtained as a slightly brown amorphous powder (yield 69%).

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.83 (2H, doublet, J = 9 Hz); 7.22 (2H, doublet, J = 9 Hz); 6.98 -6.95 (2H, multiplet); 6.75 (1H, multiplet); 6.72 (1H, broad multiplet); 6.25 (1H, doublet, J = 2 Hz); 4.84 (2H, broad singlet); 2.23 (3H, singlet); 2.19 (3H, singlet); 2.17 (3H, singlet).

Mass spectrum (EI) m/z: 340 [M⁺].

[EXAMPLE 79]

10 2-(3-Chloro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

1) N-(3-Chloro-4-methoxybenzylidene)-4-sulfamoylaniline

Following a procedure similar to that described in Example 1-1), but using 3-chloro-4-methoxybenzaldehyde and 4-sulfamoylaniline as starting materials, the title compound was obtained as a pale yellow powder (yield 72%).

15 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

8.37 (1H, singlet); 8.00 (1H, doublet, J = 2 Hz); 7.93 (2H, doublet, J = 9 Hz); 7.77 (1H, doublet of doublets, J = 2 & 9 Hz); 7.24 (2H, doublet, J = 9 Hz); 7.09 (1H, doublet, J = 9 Hz); 6.90 (2H, broad doublet, J = 5 Hz); 3.99 (3H, singlet).

20 2) 3-Chloro-4-methoxy-α-(4-sulfamoylanilino)phenylacetonitrile

Following a procedure similar to that described in Example 1-2), but using N-(3-chloro-4-methoxybenzylidene)-4-sulfamoylaniline [prepared as described in step 1)] and trimethylsilyl cyanide as starting materials, the title compound was obtained as a slightly yellow powder (yield 64%).

25 Nuclear Magnetic Resonance Spectrum (270 MHz, hexadeuterated dimethyl sulfoxide) δ ppm:

7.76 - 7.46 (4H, multiplet); 7.02 (1H, doublet, J = 9 Hz); 6.80 (2H, doublet, J = 9 Hz); 6.71 - 6.58 (1H, broad multiplet); 6.44 - 6.27 (2H, broad multiplet); 5.57 (1H, broad doublet, J = 8 Hz); 3.94 (3H, singlet).

30 3) 2-(3-Chloro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole

Following a procedure similar to that described in Example 1-3), but using 3-chloro-4-methoxy-α-(4-sulfamoylanilino)phenylacetonitrile [prepared as described in step 2)] and

methacrolein as starting materials, the title compound was obtained as a slightly yellow powder (yield 37%), melting at 160 - 163°C.

Nuclear Magnetic Resonance Spectrum (270 MHz, CDCl₃) δ ppm:

7.86 (2H, doublet, J = 9 Hz); 7.23 (1H, doublet, J = 2 Hz); 7.23 (2H, doublet, J = 9 Hz); 6.84 (1H, doublet of doublets, J = 2 & 9 Hz); 6.78 (1H, doublet, J = 9 Hz); 6.73 (1H, broad multiplet); 6.25 (1H, doublet, J = 2 Hz); 4.83 (2H, broad singlet); 3.88 (3H, singlet); 2.17 (3H, singlet).

Mass spectrum (EI) m/z: 376 [M⁺].

[EXPERIMENT 1]

Inhibitory Activity on Cyclooxygenase-1 from Ram Seminal Vesicle Microsomes (RSVM) and Human Recombinant Cyclooxygenase-2 (In Vitro Test)

In order to prepare cyclooxygenase-1 (COX-1) microsomes, ram seminal vesicles were homogenised by a blender. To prepare cyclooxygenase-2 (COX-2) microsomes, an expression vector which contains the human COX-2 gene was introduced into COS cells. The cells were homogenised by sonication after 66 hours cultivation. Microsomes were then prepared in accordance with conventional methods.

Enzyme activity was assayed as follows.

The assay mixture contained 10 μ l of COX-1 or COX-2 microsomes (5 to 15 μ g), 2 μ l of sample dissolved in dimethyl sulfoxide, 50 μ l of 200 mM Tris (pH 7.6), 10 μ l of 20 mM reduced glutathione, 10 μ l of 10 mM epinephrine, and 15.5 μ l of distilled water. After preincubation at 37°C for 15 minutes, 2.5 μ l of 10 μ M arachidonic acid (dissolved in ethanol) were then added to the mixture (final volume of 100 μ l) and allowed to react at 37°C for 30 minutes. The final dimethyl sulfoxide and ethanol concentrations were 2% and 2.5%, respectively. To the reaction mixture were then added 15 μ l of ice-cooled 0.2 M HCl to stop the reaction, and the mixture was cooled at 4°C for 5 minutes. 15 μ l of a 0.2 M aqueous solution of sodium hydroxide were then added to the reaction mixture to neutralise the pH. The amount of PGE₂ in the reaction mixture was measured using a commercially available ELISA kit (Cayman). IC₅₀ was calculated from the regression line determined by the inhibition rates of PGE₂ formation and the concentrations of the compound.

In this test, the compound of the present invention exhibited excellent inhibitory effects selective for cyclooxygenase-2.

[EXPERIMENT 2]

Inhibitory Effect on Cytokine Production in Human Peripheral Monocytes (In Vitro Test)

(1) Peripheral blood was collected from healthy human volunteers in the presence of heparin. After mixing it with an equal volume of phosphate-buffered saline (PBS, Nissui Pharmaceutical), the mixture was layered onto Ficoll Paque medium (Pharmacia) at the rate of 2:1 and centrifuged at 520 x g at 25°C for 20 minutes. After centrifugation, the monocyte layer was removed and suspended in RPMI 1640 (Nissui Pharmaceutical) containing 10% fetal calf serum (FCS). The monocytes were washed once with the same medium, placed in a plastic Petri dish, pre-treated with human plasma and incubated for 2 hours in the presence of 5% CO₂ to cause them to adhere to the dish. After incubation, the Petri dish was washed twice with PBS to remove the non-adherent cells. Thereafter, PBS containing 5% FCS and 0.2% EDTA was added to the Petri dish and the dish was allowed to stand undisturbed for 15 minutes at 4°C. The monocytes were recovered from the dish by pipetting. The cells were finally suspended in RPMI 1640 at a concentration of 1.25×10^5 cells/ml.

(2) Culture of Human Monocytes

A 40 µl solution of the test compound and 40 µl of lipopolysaccharide (LPS; E. coli, 0.26:B6, Difco), adjusted to a final concentration of 10 µg/ml, were added to 320 µl of cell suspension. The resulting mixture was then cultured for 20 hours in the presence of 5% CO₂ and the supernatant was removed at the end of cultivation to assay IL-1β and TNFα. The test compound was dissolved in dimethyl sulfoxide and diluted by a factor of 100 with FCS to reach 10 times the final concentration (the final concentrations of dimethyl sulfoxide and FCS were 0.1% and 10%, respectively).

(3) Measurement of Cytokine in the Supernatant Medium

The amount of IL-1β was measured with a commercially available ELISA kit (Cayman), after diluting the supernatant medium by a factor of 15 or 30 with the ELISA buffer. The amount of TNFα was similarly measured by a ELISA kit (Genzyme) after diluting the supernatant by a factor of 2.

In this test, the compound of the present invention exhibited excellent inhibitory effects on production of inflammatory cytokine.

[EXPERIMENT 3]

Analgesic effect using Randall-Selitto method (In Vivo Test)

(1) Test Compound

The compound was suspended in 0.5% tragacanth and administered orally at a volume of 5 ml/kg. The control group was administered with 0.5% tragacanth only as a vehicle.

5 (2) Animals

Wistar-Imamichi rats (males, 5 week old, body weights: 80-100 g) were used in this test.

(3) Test Method

The test was conducted in accordance with the method of Winter and Flataker [J.

10 Pharmacol. Exp. Ther. 150, 165-171, (1965)], which is a modification of the original method of Randall and Selitto [Arch. Int. Pharmacodyn. Ther. 111, 405-419, (1957)]. The rats were fasted for 16 hours prior to use. Inflammation was induced by subcutaneous injection of 0.1 ml of a suspension of 20% beer yeast (Sigma) into the right hind footpad of the animal. After 4.5 hours, increasing pressure was applied to the inflamed footpad at a constant speed using
15 an Analgesy meter (Trade mark) (Ugo-Basile Co.). The pressure at which the animal exhibited a squeaking reaction was measured and considered to be a pain threshold (units: g). To those rats that exhibited a pain threshold of less than 200 g (mean: 60 to 120 g), the compounds were immediately administered orally and pain threshold values were measured 0.5, 1 and 2 hours after administration.

20 First the average of pain threshold values at each time point (0.5, 1, and 2 hr) was calculated in a control group. If a pain threshold value exceeded 2 times the control average value at the same time point even once in the drug-treated groups, then the animal was considered to indicate efficacy. Efficacy rates of the drug were estimated by the evaluation method of Blake [J. Pharm. Pharme. 19, 367-373, (1967)]. The results are shown in Table 3.

25

Table 3 Analgesic effect using Randall-Selitto method

| Example No. | Efficacy Rate (No. of animals in which drug was effective/No. of animals used in test) |
|----------------|---|
| | Dose: 12.5 mg/kg |
| 7 | 5/5 |
| 18 | 5/5 |
| 19 | 5/5 |

| | |
|----|-----|
| 52 | 5/5 |
| 62 | 5/5 |
| 65 | 5/5 |
| 66 | 5/5 |
| 67 | 5/5 |
| 69 | 5/5 |
| 71 | 5/5 |
| 77 | 5/5 |
| 78 | 5/5 |
| 79 | 5/5 |

[EXPERIMENT 4]

Carrageenan-induced Paw Edema Test (In Vivo Test)

The same test compounds were subjected to the test as those in the Randall-Selitto method. Wistar-Imamichi rats (males, 6 week old, body weights: 110-120 g) were used in this test.

The method of Winter, *et al.* [Proc. Soc. Exp. Biol. Med. 111, 544-547, (1962)] was slightly modified to perform the test [Sankyo Annual Research Report 39, 77-111, (1989)]. The rats were fasted for 16 hours prior to use. Inflammatory edema was induced by the subcutaneous injection of 0.05 ml of a 1% carrageenan (Viscarin 402) solution into the right hind paw of the animal. The test compounds were administered orally 30 minutes before injection of carrageenan. The volume of the right hind foot was measured with a Plethysmometer (Trade mark) (Ugo-Basile Co.) just before administration of the test compound and 3 hours after injection of carrageenan to determine the edema intensity [(right foot volume after 3 hours/right foot volume before injection) - 1]. The inhibition rate (percentage) at each dose was calculated and is shown in Table 4.

Table 4 Inhibitory effect on Carrageenan-induced Paw Edema in rats

| Example No. | Inhibition Rate (%) Dose: 50 mg/kg |
|-------------|------------------------------------|
| 7 | 56 |
| 17 | 67 |

| | |
|----|----|
| 18 | 53 |
| 19 | 65 |
| 41 | 60 |
| 52 | 65 |
| 62 | 55 |
| 64 | 60 |
| 69 | 55 |

[EXPERIMENT 5]

Scald-induced Pain Test (In Vivo Test)

The test was conducted in accordance with the method of Iizuka and Tanaka [Jpn. J. Pharmacol. 70, 697, (1967)]. The test compound was administered in the same manner as in Experiment 3. Male Wistar-Imamichi rats (4-5 week old, body weights: approximately 100 g) were used after fasting for 16 hours. The right hind foot of the animal was immersed in hot water at 57°C for 6 seconds to induce scald under ether-anesthesia. Two hours later, the scald foot of the rat was irritated by immersing in hot water at 40°C for 5 seconds, and the animal was returned to the cage.

The behaviour of the animal was observed for 30 seconds. Lifting up the scalded foot or licking it without coming in contact with the metal cage were considered to be pain responses. Pain response time was determined as the total time of the pain response during the 30-second observation period. After selecting only those animals that exhibited a favorable pain response two hours after inducing scald, the animals were given a test compound by oral administration. Pain response time was again measured 1 and 2 hours after dosing and the mean value was determined. Using the mean values, inhibition rates were calculated relative to the control group.

These results are shown in Table 5.

Table 5 Analgesic effect on scald-induced Pain in rats

| Example No. | Inhibition Rate (%) Dose: 20 mg/kg |
|-------------|------------------------------------|
| 52 | 89 |

[EXPERIMENT 6]

Antipyretic effect on yeast-induced fever (In Vivo Test)

The method of Roszkowski et al. [J. Pharmacol. Exp. Ther. 179, 114, (1971)] was slightly modified to perform the test. The test compound was administered in the same manner as in Experiment 3. Male Wistar-Imamichi rats (6 week old, body weights: approximately 120 g) were used in the test. Yeast (Brewer's yeast, Sigma) was suspended in physiological saline to a concentration of 25%, finely crushed in an agate mortar, and injected subcutaneously into the backs of the rats under ether-anesthesia at a volume of 2 ml/rat. The rats were fasted after the injection of yeast. On the following day (19 hours after the yeast injection), a catheter-type thermistor thermometer (Japan Kodan, MGA III) was inserted approximately 5 cm into the rectum to measure the temperature of the animals. Those animals, which exhibited a fever of 1.5°C or more compared to normal animals, were selected, and grouped so that the mean fever temperatures of each group were nearly equal. Rectal temperatures were measured 1 and 2 hours after administration of the test compound, and fever temperature was calculated by subtracting the normal temperature of healthy animals measured simultaneously. Inhibition rate of the group treated with the compound relative to the control group was calculated by using the mean value at 1 and 2 hours after dosing. These results are shown in Table 6.

Table 6 Antipyretic effect on yeast-induced fever (In Vivo Test)

| Example No. | Inhibition Rate (%) Dose: 0.4 mg/kg |
|-------------|-------------------------------------|
| 52 | 82 |

08-083562

Name of Document
Document to be amended

Date to be amended by authority
Patent Application

Recognition information & Addition information

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